INTERNATIONAL ABSTRACT OF SURGERY

VOLUME 71 SEPTEMBER, 1940 NUMBER 3

SPECIAL CONTRIBUTION

THE ETIOLOGY OF PRIMARY RENAL CALCULUS

ALEXANDER RANDALL, M.D., F.A.C.S., Philadelphia, Pennsylvania

"Common sense and worldly experience tell us that if we would overthrow an enemy we must understand all his resources; if we would overcome a difficulty we must understand where the difficulty resists our attempts; if we would solve a problem, the nature of the problem must be understood. The principle underlying these statements should be applied in the prevention and cure of disease."—SIR JAMES MACKENZIE.

PART I. INTRODUCTION

WHEN one undertakes to discuss the etiology of renal calculus, one can either indulge in a critical analysis of the evidence supporting the various etiological theories, or else be very explicit, dealing only with what one considers to be the pertinent facts.

Thoughtful physicians throughout the ages have tried to reason out an answer to the centuries-old riddle of the etiology of stone. Climatic surroundings have been suspected, racial susceptibility and heredity blamed, geographical districts held responsible, age criticized, sex analyzed, drinking water incriminated, personal habits examined, and even the texture of the skin held responsible. But scientific medicine has not been able to accept any of these generalities as in any way answering the question, nor in anywise aiding preventive therapy. These ideas have been so frequently presented, and so well expounded in the past, that I wish to be allowed to omit such entirely in my approach to the subject, and to restrict this presentation to a brief exposition of the scientific research work of the past ten years.

From the Department of Urology, the Department of Research Surgery, and the Wistar Institute of Anatomy, University of Pennsylvania, and the Laboratories of the Abington Memorial Hospital and the Philadelphia General Hospital.

This of necessity will require a restatement of some of the research problems that I have attempted and the relationship which they bear to research work elsewhere.

It is quite evident to any one familiar with the literature that a gradual change in our point of view has transpired during recent years. Renal stone has been treated in the past as a disease entity, based upon certain (but not known) causes. This attitude has been especially hard to correlate with the known and varied distribution of the condition and the wide diversity in the chemical composition of calculi. Of late a change from this point of view has been forced upon us, a realization that stone is, and has to be, only a symptom. This, in turn, has forced the realization that there then has to be a pre-calculus lesion and that perhaps the variation in the chemistry of stone is only incidental. There has been coined a new word, "calculogenesis" to cover this entire problem of the growth of a calculus, and research of late has been striving to find and to prove the various stages that antedate the well known clinical state in which a calculus is producing, for the first time, active and alarming symptoms.

GENERALITIES

Clinically, a renal calculus is recognized only after its growth has reached what might be called its maturity. That this growth has consumed time hardly requires any argument, and that symptomatic silence is the rule during this time is likewise evident. Nevertheless, in a great many articles of the past the idea seems to have been accepted that the time element between a stone's

origin and the development of clinical symptoms was of no importance, or else that the time required for growth was very brief. That this one point alone is of the utmost importance should be stressed, for the facts are only too self-evident that the growth of a calculus is extremely slow, and because of this any explanation of calculogenesis must account for this period of symptomatic silence.

Clinically, cases of renal calculus have been classified as primary or secondary, and as these terms have been differently applied, their definition as used here is necessary. *Primary renal calculi* infer those for which no apparent causal factor—in the kidney, pelvis, or ureter—can be clinically recognized; i.e., no renal abnormality, no obstructive uropathy, no recurrent hematuria, no persistent infection, and no recognized metabolic fault; all of which are definite and well recognized pathological conditions in which crystal formation and deposition may logically occur and a calculus grow. *Secondary renal calculi* include those for which such causal factors do exist and can be clinically recognized. From another point of view, a secondary renal calculus is one for which the clinician or surgeon can recognize a pathological or physiological fault and feel certain that its correction becomes an essential step in the cure and the prevention of the recurrence of stone. These cases of secondary renal calculus, complicated as they are with other recognized physiological or pathological conditions, must be put aside from this study, as they only confuse the essential picture of the etiology of simple primary renal calculus.

It is the elucidation of the etiology of the primary renal calculus that engrosses us today, as we know full well that over 50 per cent of the cases of renal stone fail to present clinical evidences as to why they occur after the most careful scrutiny by all the diagnostic means at our disposal. To make this point unquestionably clear, I refer, in speaking of primary renal calculus, to the patient who presents himself at the clinic in his first sudden attack of ureteral calculus colic, who shortly thereafter passes per urethra a typical renal calculus, and yet who, on the most careful and painstaking study, presents no cause or reason why he suffered therefrom, and the surgeon is completely baffled to give any advice that might prevent a recurrence of the painful malady.

If we are to explain the cause of renal calculus, it becomes evident that it is in this simple group of primary calculi, uncomplicated by secondary factors, that our answer lies, while at the same time the apparent simplicity of the problem, its uncomplicated picture, and its clinical importance all challenge our most thoughtful endeavors. It is to this problem alone that this paper is devoted.

It has been well said that an intelligent approach to any research problem may be gained "by asking mother nature simple questions one by one," and I believe we can clear up a great many misunderstandings, and proceed on a common ground of knowledge, by an analysis at this time as to what are the evident and recognized fundamentals of our problem.

In the first place, it is self-evident that such a primary renal calculus has its origin within the limits of the renal pelvis, including both major and minor calyces. This excludes a true renal origin; i.e., an origin within the renal structure, excepting perhaps the very terminal portions of the collecting ducts in the tips of the renal papillæ.

Secondly, in the absence of urinary obstruction (and I mean demonstrable obstruction by investigative methods of today), it becomes absolutely essential that any etiological explanation must take into account where the calculus resided while attaining growth, for otherwise it would not remain for long within the pelvis, but be expelled while still of minute size.

Thirdly, primary renal calculi (with very rare exceptions) are composed of salts normally present in normal urine: there are no evident extraneous factors present.

Fourthly, the chemical composition of stone, varying as it does between eight or more salts, gives nothing especially characteristic in form or structure that suggests its origin, other than those characteristics typical under the laws of crystallization, and for the individual salt present.

SPECIALITIES

Such generalities are easily agreed upon, and we can proceed to a closer questioning of certain features, the most interesting of which is to determine an acceptable reason to account for the element of time during which a stone gains its growth. A specific case will illustrate this point:

A woman was examined by means of a roentgenogram in 1934 (Fig. 1), in search for a cause of left-sided backache, and a small, triangular shadow was observed within the outline of the lower pole of the right kidney and thought to be a renal calculus. A second picture was taken in 1935, and the shadow was observed unchanged. Again, in 1937, another picture was taken (Fig. 2), and, although the position of the shadow was unchanged, there was a slight increase in size and density. There having been no symptoms there-

from in this interval of three years, it was decided to prove whether or not it was a renal calculus. An intravenous urogram (Fig. 3) left no doubt that it was such and that it was situated in one of the inferior minor calyces, and that otherwise the kidney pelvis was normal. One and a half years later an acute attack of right renal colic occurred. In seventy-two hours the shadow was in the lower third of the ureter (Fig. 4), and after two cystoscopic manipulations the calculus was passed per urethra, still showing its characteristic triangular shape.

Experiences such as this—and they are not uncommon—present the most important deductive evidence:

First, it was without question that the calculus had its origin, and subsequently grew during four and one-half years of observation, attached to some portion of a minor calycine structure, and during this interval presented no symptoms. Once freed from its attachment, and in a few days, the body had rid itself of this calculus. Let me accentuate two things of great importance: (1) the long interval of time during which it was *known* to be present; and (2) its absolutely asymptomatic existence!

A second deduction is permitted—that there must have been some reason why that calculus formed at that point—and one must assume an initiating lesion to have existed there prior to the stone's crystallization.

A third deduction may be stated, for not only in this case, but in many similar instances, roentgenographic studies leave little doubt that these typically primary renal calculi take their origin within the shadow outline of a minor calyx, and, therefore, the precalculus lesion must occur thereabouts.

A fourth deduction may be permitted—that the lesion which acts as the nidus for the crystallization of common urinary salts thereon would most likely occur upon the actively functioning renal papilla, rather than upon the simple lining membrane of a minor calycine wall.

And so, it becomes increasingly self-evident that such a stone has to be the product of a localized morbid process which antedated the period of salt crystallization and true calculus formation. Such I have termed the *initiating, or precalculus, lesion.* Everything points to it; every known fact strongly suggests it: every pertinent question demands it; the laws of crystallization are nullified in its absence; and pathology itself is incomplete without it.

I believe that for a successful research explaining the etiology of primary renal calculus, we must cease to think in terms of a clinical condition and train ourselves to think in terms of morbid anatomy. I consider such a change of approach the most far-reaching concept in the entire problem.

With these self-evident facts as a guide, in 1929 we began a series of experimental research problems in animals in an effort to create such an initiating lesion, with the hope that we would be able to observe calculi grow thereon. These problems have been published elsewhere (Randall, 1937), and it is only necessary at this time to report either failure in some of the problems, or such inconsistent results in others as to make further pursuit futile.

There was one small study, however, that gave valuable positive evidence. It was thought that if stone grew upon and from some mural lesion, visible evidence of this attachment should be recognized on magnification and study of such stones. A group of 265 calculi were studied, all of which had been voided per vias naturales, or removed by ureterolithotomy, and the time element had been short between the onset of colic and delivery from the body. A visible facet, giving unquestioned evidence of mural attachment, was present in 106, or 40 per cent, of these specimens. Such appeared generally as a smooth area on the surface of a highly crystalline calculus, and often was depressed, with the edges encroaching and overhanging. It was frequently observed to be of a different color, and suggested a different composition. Magnification increased the presumptive evidence that this was the stoma, or facet, of original mural attachment.

It was during these formative years, though marked by many experimental disappointments, that our hypothesis of the necessity of a precalculus, or initiating, lesion became stronger and stronger, and two postulates were written which it was hoped in the end we would be able to verify and prove; to wit:

1. That there must always be an initiating lesion which precedes the formation of a primary renal calculus.

2. That such an initiating lesion was to be looked for on the renal papilla.

A search of the literature for the then known pathology of the renal papilla was most disappointing. The hemorrhagic papillitis of Fenwick, the uric-acid infarcts of the newborn, the calcium infarcts of Henle (Lubarsch), and the occurrence of tuberculous ulcerations (Lieberthal) cover about all that had been recognized by the pathologists as primary lesions. I do not wish to slight numerous isolated observations of various

individuals reporting odd cases. I have not found any that related their observations to the wide problem of calculus disease, and I refer more to accepted teachings as outlined in the books on gross and microscopic pathology. In fact, the survey of this literature left one with the distinct feeling that the pathology of the renal papilla was yet to be written.

It was therefore felt that any research directed toward an understanding of the etiology of primary renal calculus should try:

1. To establish the existence of an initiating lesion.
2. To demonstrate that stone will, and does, develop thereon.
3. To explain the pathology of such an initiating lesion.
4. To deal with an appreciation of the reasons why such a lesion develops, its cause, and perhaps its prevention.
5. To relate these observations to the existing theories, through animal experimentation.
6. To point out such preventive measures as may be expected to bear results.

Part II. Research on the Etiology of Primary Renal Calculus through Autopsy Studies

As our animal experimental efforts had given negligible results, it was decided to go to the autopsy table and, by dissecting out each minor calyx to the complete exposure of its individual papilla, to uncover whatever observations awaited us, and to hope that time, patience, and industry would reward our efforts by possibly showing us lesions that could be related to stone's origin and growth and, perhaps, to the actual finding of early crystalline deposits. In other words, instead of trying to *create* stone experimentally by following theoretic dogma, we turned to trying to *find* stone as it occurred in man, to observe it in its incipiency, to record its point of origin and to study microscopically its causal factors. The co-operation of the Department of Pathology at both the Hospital of the University of Pennsylvania and the Abington Memorial Hospital made this effort possible, and at my request each put at my disposal the kidneys from all autopsies, to be opened and sectioned as we saw fit. Each kidney was examined by first opening the pelvis, and from it, by careful dissection, each major and minor calyx was laid open in turn and each papilla completely visualized and studied with a hand lens. After six months the large autopsy material from the Philadelphia General Hospital was added, greatly amplifying our opportunities.

TABLE I.—RESULTS OF AUTOPSY STUDIES

Date	Total number of autopsies	With calcium plaque		Primary renal calculi	
		Number	Per cent	Number	Per cent
May 1, 1936	104	12	11.5	3	2.8
Dec. 4, 1936	298	28	9.4	8	2.7
Feb. 15, 1937	429	73	17	28	6.5
May 15, 1937	609	140	22.9	49	4.1
Dec. 1, 1938	1154	227	19.6	65	5.6

Starting in December, 1935, there have been examined to date (December 1, 1938) 1,154 pairs of kidneys. Two hundred and twenty-seven individuals, or 19.6 per cent, have shown calcium-salt deposition, either unilateral or bilateral, of one or more of the renal papillæ, and 65 individuals revealed a primary renal calculus growing upon and attached to a renal papilla. The statistical progress of this research is presented to illustrate the consistency of our findings as tabulated and reported at varying intervals and with our increasing experience.

TABLE II.—678 CONSECUTIVE AUTOPSIES

Age	Autopsies	Plaques	Per cent	Stones	Per cent
10–19	27	1	3.7	0	0.0
20–29	41	4	9.7	2	4.8
30–39	79	11	13.9	2	2.5
40–49	94	18	19.1	3	3.1
50–59	124	14	11.2	3	2.4
60–69	142	29	20.4	4	2.8
70–79	130	21	16.1	7	5.3
80–99	41	4	9.7	0	0.0

Our interest has centered particularly about what might be called the minor pathological changes, and kidneys showing gross destructive pathology—pyonephrosis, advanced tuberculosis, —are not included at all. In other words, kidneys heretofore passed as having normal pelves have been the ones we particularly searched for early papillary lesions.

Papillary Lesion Type I. The Calcium Plaque

Starting our post-mortem series we examined 27 normal kidneys before encountering our first papillary lesion. This lesion was so innocent in appearance, and yet so definitely abnormal when compared to our previous observations, that it demanded attention. There was present a cream-colored area near the tip of a renal papilla, which was definitely not on the surface, but appeared to be subsurface or subepithelial. Shortly thereafter we found 4 kidneys that showed similar lesions—some with a deposit in only 1 papilla, others with involvement of several papillæ, some with uni-

lateral involvement, others showing bilateral papillary involvement. On microscopic study the lesion was found to be a plaque of calcium salts deposited in the interstitial tissue of the renal papilla, and definitely not intratubular. In places, rings of calcium salts were to be seen, where deposition had occurred in the collagenic membrane of the collecting tubules, and where such were in close proximity, interstitial deposition created solid masses visible to the naked eye. Special microscopic stains were used to identify this material as calcium, and sufficient was collected by teasing out such plaques for chemical analysis and proved to be composed of salts of calcium. Dr. James H. Jones of the Department of Physiologic Chemistry of the University of Pennsylvania analyzed 4.65 mgm. of such material for me, to find calcium to occur in 4.967 per cent (5 per cent). As muscle, liver, lung, and kidney contain only from 0.1 to 0.5 per cent, it left little doubt that calcium was present in high concentration. Dr. Charles G. Grosscup of the Abington Memorial Hospital, with 1.9 mgm. of material, composed of plaques carefully teased from visible papillary lesions and carefully separated from all organic material, undertook a quantitative analysis. He reported that the material was microcrystalline and chalky in appearance, was insoluble in water and acids, but dissolved in alkalies. Quantitatively, calcium was present in 19 per cent, nitrogen in 10 per cent, carbon dioxide in 1 per cent, and phosphorus was present, but it was difficult to estimate the amount accurately. He stated, "In view of the low CO_2 and phosphorus content and the high calcium (19 per cent) it is evident that about 80 per cent of the calcium must be bound in some other form. With the murexide text indicating xanthine, the insolubility of the material in acids, and the high non-protein nitrogen, I suggest that this may be nucleic acid."

It is my wish at this point to emphasize especially that this lesion, or morbid process, as we have found it, occurs particularly in the walls of the renal papilla—some are centrally placed, some just subsurface; that it is not essentially an intratubular deposit, but a broad plaque of calcium-salt deposition invading and replacing interstitial tissue (Fig. 5); that, from our studies, its first deposition is in the collagenic, or basement, membrane of the walls of the collecting tubules, from which it gradually involves the intertubular spaces and causes the tubules gradually to shrink, to lose their lining cells and disappear, or to remain with markedly narrowed lumens; that in the many sections which we now have studied, of practically all the lesions mentioned, in only 9 (3.9 per cent) have there appeared cellular destruction and round-cell infiltration, which could be interpreted as evidence that infection accompanied this calcium-salt deposition. These exceptions I consider as the inevitable finding when taking such material from the autopsy table, and believe that it represents a secondary factor where infection has been implanted upon a pre-existing pathological condition.

Early in the series a kidney was found with four of the seven papillæ containing calcium plaques, and on one such calcium plaque a secondary deposit of some black material could be seen. This deposit was about 1 mm. in diameter and quite distinctly visible (Figs. 6 and 11). Microscopic sections of this specimen showed evidence that, through increasing growth and pressure, this calcium plaque had lost its epithelial covering, and on its surface was being deposited a layer of some different material that was black in color. Its minute size defied chemical analysis and specific staining methods; but from our subsequent studies we now look back upon this tiny speck as the earliest evidence of renal calculus formation ever seen and recorded as such.

The next important step in calculogenesis was observed with the examination of a kidney in which a small stone was found, which was, however, unfortunately dislodged by the knife as the kidney was opened. Search of this same kidney, however, revealed another papilla which contained a visible calcium plaque supporting a second stone which projected into the lumen of the minor calyx (Figs. 7 and 8). This stone was firmly adherent, measured approximately 2 mm. in diameter, and resembled in appearance the larger calculus which the knife had dislodged. Study of these specimens has been most valuable: in the first place the dislodged stone has been analyzed and proved to be composed of calcium phosphate; microscopic sections of the adherent stone have demonstrated unquestionably that it is growing from, and is supported by, a typical calcium plaque imbedded in the wall of the renal papilla; special stains have shown that this stone is also of calcium phosphate, while the plaque itself is composed of calcium but does not show, on specific staining, phosphate as a salt. So here we have a definite renal calculus growing on an initiating lesion of the papilla, and while the lesion is a deposition of one calcium salt in the walls of the renal papilla, the calculus is composed of a totally different calcium salt.

The demonstration of this fact just stated—that the two are distinctly composed of different salts of

calcium—becomes a most vital factor in our conception of the origin of renal calculus, and is to be emphasized. Here, for the first time, we find a lesion of not infrequent occurrence (19.6 per cent) and of rather constant character and chemical composition. This lesion, innocent enough while buried in the wall of a renal papilla, can lose its epithelial covering and from then on be bathed in calycine urine, and then, acting as a foreign body, it becomes the nidus upon which a different urinary salt crystallizes. Here, likewise, we can picture the reason that renal calculi can remain stationary while increasing in size. Here we can account for a common origin of stone formation, which also allows of the known variation of salts so deposited to form stone, and we can assume that the salt which crystallizes to form a calculus is the one which, at that epoch, is most readily precipitated from solution. Study of the serial sections through this stone has likewise shown us, at the edge of the plaque, a definite elevation of the plaque by the encroachment of crystallization, which suggests that when a stone becomes free, it does so by tearing the plaque from its tissue bed and taking it away with it. This quite corroborates our observation mentioned before: a visible facet or stoma in 40 per cent of 265 primary renal calculi.

From this point on our studies have taken a variety of directions, most of which have been published in one form or another, and I wish to recount here only the final figures and the essential microscopy. *We have observed to date 65 kidney specimens in which calculi have been seen growing upon papillæ.* Thirty-one of these have had a single stone present, while in 10 specimens two papillæ were found with stones adherent, and varying combinations make up the remainder, including 10 instances of tiny black deposits, less than 1 mm. in diameter, that have repeatedly shown us the earliest evidence of beginning secondary deposition upon the fundamental or primary lesion of papillary calcium salt deposit; i.e., upon the calcium plaque.

It had been our purpose to try to demonstrate that each calculus as found was supported by a primary intrapapillary calcium plaque as its initiation lesion. The extreme difficulty of this will be readily understood. In the first place such calculi have to be properly decalcified before sectioning—not completely decalcified, of course, but enough to allow sectioning—and in doing this we lost specimens. Again, we tried to depend upon special stains in an effort to differentiate the various possible salts. This required special methods of tissue fixation, which, in turn, dissolved some specimens, and others were made so brittle as to be completely fragmented on sectioning. In addition, it has been difficult, and most tedious, to attempt complete serial sectioning of stones 6 and 8 mm. in diameter in order to cut through the stone and its possible underlying plaque, which frequently is minute and generally eccentrically placed.

In order to avoid these disappointments, three other procedures have been adopted in order to prove that each calculus arises from a calcium plaque in the wall of a papilla. First, a few selected specimens have been subjected to tissue-clearing methods, and by this means we hoped to visualize through the cleared papillary wall the underpinning of the calculus upon the papilla's surface. This proved unsatisfactory at first, as the tissue-clearing solutions dissolved the calculi too readily. We shall be able, I believe, to circumvent this in the future, and I hope to be able to so demonstrate a calculus and its intrapapillary plaque foundation.

The second method was discovered accidentally when a tiny black stone, 3 mm. in diameter, was inadvertently dislodged. On examining it under a strong lens, it was distinctly seen to be composed of a black mass with a bossed surface, simulating the early jackstone development of the calcium-oxalate stone, but on one surface a clear-cut white layer was attached, distinctly different and definitely crystalline: this we inferred to be the calcium plaque. Through the co-operation of Dr. A. Newton Richards these two layers were analyzed separately. The calculus weighed 5.5 mgm. (Fig. 9). Microchemical analysis was made, which showed that the white layer, or calcium plaque, was composed of calcium carbonate, with a decided trace of calcium phosphate. The black stone gave a negative test for calcium carbonate, calcium phosphate, and uric acid, but was conclusively proved to be pure calcium oxalate. *This is a most significant finding, for here again, on a papillary plaque composed of calcium carbonate and calcium phosphate, a stone composed of a different salt, calcium oxalate, has formed.* Two other calculi of similar character have been gently dislodged from their papillary attachments, and in each case the white plaque is plainly visible. This, to a degree, suggests and strengthens the assumption that, as a calculus is extruded in life, it gains its freedom by tearing away its supporting plaque from its original tissue bed. Such is to be observed in one of our specimens subjected to microscopic section, in which can be seen the crystalline material burrowing under the edge of the calcium plaque and elevating it from its papillary-tissue bed (Fig. 10), which gives micro-

scopic proof that a primary renal calculus gains its freedom by tearing away the calcium plaque on which it grew.

The third method of proof arose through the x-ray study of a known uric-acid calculus. This calculus has long evaded our efforts to prove that it had a similar origin upon a primary papillary plaque. Decalcification for microscopic sectioning, as in the calcium-phosphate stone, is, of course, utterly out of the question. Microchemical analysis, as in the calcium-oxalate calculus, of a long series of stones as found at autopsy, in the hope that chance would favor us, was also asking too much, both of our chemical friends and of chance itself. However, chance did favor us in an unexpected way, and proof was forthcoming from a clinical study, substantiated by a restudy of previous clinical cases and by chemical analysis.

A patient presented himself at the clinic with left renal colic, and on study a diagnosis was made of a large x-ray negative stone occupying the right renal pelvis, while on the symptom-bearing left side a small stone completely blocking the left ureteropelvic junction could be recognized. Operation was performed for the removal of the small stone on the left, following which the stone was roentgenographed by itself. Figure 10a is a print from the plate obtained. One recognizes in this picture the shadowy outline of the true uric-acid calculus, the same having been subsequently analyzed and proved of such a chemical nature, while in the center of this shadow is seen the dense outline of a second salt. This finding sent us back to our collection of specimens, and in 5 other uric-acid stones a similar inclusion has now been demonstrated. This led us directly to a sectioning of the calculus and a chemical analysis of its included dense shadow, which proved it to be a calcium salt positive for calcium carbonate and calcium phosphate. Here, then, we have substantiating evidence that a third type of primary renal stone was formed from a salt of a different chemical nature from the plaque on which it grew, and it was recognized by a third means of identification, i.e., roentgenology.

Thus, we have three distinct and different chemical salts, each forming characteristic primary renal calculi and each representative of the frequent clinical cases, which are now proved to have their origin from an initiating lesion in the renal papilla. It is to be hoped that the rarer and unusual salts which form stone will, in time and in their turn, be found to have a similar origin.

While these researches have been furthered in an effort to substantiate the idea of a papillary initiating lesion, and to prove quite definitely the rôle played by the calcium-plaque formation and its relationship to the clinical occurrence and growth of a renal calculus, we have been keenly interested also in trying to solve the *raison d'être* of the deposition of calcium salts in the wall of the renal papilla. Many specimens have been sectioned for microscopic study, and the pathology as we have interpreted it follows. One need not accentuate the prevalence of calcium-salt deposition in many parts of the body in response to tissue damage and repair. The writings of H. G. Wells and the recent excellent article on "Calcification and Ossification of the Kidney" by Goldstein and Abeshouse cover this ground thoroughly, and as Quinby says, "Pathology has long ago demonstrated the *early and easy* deposition of calcium in any area in which the tissues have become avascular, with fragmentation of the cells and intercellular substance." I am obliged especially to Dr. John Eiman, Pathologist of the Abington Memorial Hospital, for the following detailed description, and to Dr. Balduin Lucké, Professor of Pathology, University of Pennsylvania, for his interest and aid in obtaining special staining methods and in section cutting, as well as his coincidence with the opinions expressed on the microscopic pathology.

Microscopic pathology. Normal papilla. The normal papilla is covered by cells which differ from those lining the calyces and the collecting tubules, in that they are flat and very thin and form a single layer; they are modified cells of the lining epithelium of the collecting tubules. The collecting tubules in the papilla vary considerably in diameter, the larger ones, or the ducts of Bellini in the area cribrosa on the apex of the papilla, measuring from 100 to 200 microns in diameter. The cells lining the collecting tubules are arranged as a regular single layer, with their nuclei at one level and their free surfaces bulging slightly into the lumina. The smaller collecting tubules are lined by sharply defined cuboidal cells. As the collecting tubules grow larger, the cells become higher and in the ducts of Bellini acquire a tall columnar form. The epithelium of the collecting tubules rests upon a well developed and distinct basement membrane. The interstitial connective tissue in the papilla is more abundant than in the cortex and medulla of the kidney, and there is an abundant amorphous ground substance.

The simple calcium plaque (Fig. 5). Approximately midway between the tip and the base of the papilla, underneath the epithelial covering, is an area measuring 2.5 mm. in length and vary-

ing from 0.1 to 0.3 mm. in width, composed of dense connective tissue. The surface of the papilla over this area is somewhat irregular. The blood vessels in this location are less numerous, and those present are partially obliterated by the surrounding dense connective tissue. Some of the collecting tubules are devoid of lining epithelium, while other tubules show cells with degenerative changes. In the portion of this region nearest the papilla's tip there are a number of small areas showing granular detritus. In this location are seen two small irregular deposits of purplish-staining material (H. and E.) measuring approximately 0.3 by 0.03 mm. By special staining methods[1] these deposits prove to be calcium salts. These calcium-salt deposits, or plaques, are separated from the surface of the papilla by a thin irregular layer of connective tissue and covering epithelium. Where the calcium is less dense it occurs in rings, definitely deposited in the basement membrane of the tubules and spreading therefrom into the ground substance of the surrounding connective tissue.

Throughout the papilla, but especially near the tip, there are areas showing an increase of interstitial connective tissue. Some of the blood vessels show narrowing and irregularity of their lumina. The cortex and medulla show no noteworthy lesions. The walls of the convoluted tubules show no calcium-salt deposits. The larger vessels show a moderate degree of arteriosclerosis. *There is no microscopic evidence of infection in this specimen.*

Such is the microscopic appearance of the simple deposition of calcium salts in the renal papilla, taking the form of a shell of chalk, quite comparable to similar changes seen in the lung, spleen, or arteries, when tissue damage has occurred and reparative efforts have followed. Such deposition may occur in any part of the renal papilla, but our observations sustain the point that it is rarely diffuse, and frequently only one plaque is observed on one single papilla after close inspection of both organs. Such a plaque imbedded in the papilla, and so protected, remains innocent of any implication in the causation of stone until the succeeding stage develops.

Fully developed calcium plaque, or initiating lesion (Figs. 6 and 11). Near the tip of the papilla there is a loss of continuity of the surface with the formation of a shallow depression. In this depression is situated an irregular plaque, measuring 0.6 mm. in length and from 0.1 to 0.2 mm. in width, which by special staining proves to be composed of calcium salts. This plaque shows numerous small, roughly rounded spaces which vary in size. Over the surface of this blue-staining calcium plaque there is a distinct layer of brownish material which measures 0.025 mm. in thickness; this layer is definitely of different material from the calcium plaque. The calcium plaque is not uniform in texture; in the looser parts about the periphery the calcium salt is seen deposited in the basement membrane of partly compressed collecting tubules. There are a few tubules which show deposition of the calcium salt in some of the lining cells, while other cells are completely preserved.

Special stains of sections from this specimen show that when the calcium salt is to be deposited, it appears to be laid down first of all as fine granules in the basement membrane of the collecting tubules. With further deposition such granules coalesce until the calcification appears as a complete ring encircling the tubule, generally with loss of epithelial lining, though occasionally there can be found some viable cells. From this point the calcium salt is further deposited in the ground substance of the surrounding connective tissue, with gradual generalized coalescence and plaque formation. There is no evidence of a deposition of calcium salts in the convoluted tubules.

Near the plaque and at the tip of the papilla are seen many large, roughly rounded, irregular spaces, many of them devoid of epithelial lining, but some showing epithelial cells in different stages of degeneration. These large spaces undoubtedly are cross sections of large collecting tubules or ducts of Bellini that have lost their normal epithelial lining. Toward the base of the papilla the dilatation of the collecting tubules is less marked, and the lining shows consistently larger numbers of epithelial cells with lesser degrees of damage. *There is no microscopic evidence of infection in the specimen.*

This we have termed the fully developed initiating lesion, for here we see for the first time a brown secondary deposit, with entirely different staining properties, laid down in laminæ upon a simple calcium plaque: *the essential point is that this plaque has lost its epithelial covering, and is now bathed in calycine urine; hence the perfect nidus for crystallization exists.*

Calculus growing on plaque (Figs. 7, 8, and 10). On opening of the kidney pelvis this specimen showed a definite concretion, approximately 2 mm. in size and firmly attached to a papilla; the specimen was fixed and sectioned successfully. Sections of this specimen show in the center of

[1]The special stains used in this study are: von Kossa, Eros, Giemsa, Masson, azocarmine, elastic-tissue stain, Grandis and Mainini, methylene blue, and picric-acid stain for urates and uric acid.

the papilla near its tip irregular calcium-salt deposits over an area 2.2 by 0.6 mm.; these are deeply imbedded and far from the surface of the papilla. Lateral to this and distinctly near the surface of the papilla occurs a second calcium-salt deposit measuring approximately 0.4 by 0.1 mm.: it is a characteristic calcium plaque. Supported by this plaque and growing from it alone is an irregularly shaped calculus measuring 1.75 by 0.8 mm. A second calculus found in this kidney was analyzed and proved to be composed of calcium phosphate. The sections of this specimen, when stained by the von Kossa technique, show this calculus to be composed of calcium phosphate, but it is of particular interest that the calcium plaque shows no phosphatic staining. All methods for specific staining prove the plaque to be composed of a calcium salt, but definitely not calcium phosphate.

Here, therefore, is microscopic evidence to prove that a stone visible to the naked eye as attached to a renal papilla actually grows from an intrapapillary calcium plaque and is supported thereby, *and, furthermore, that a stone of one proved chemical composition (calcium phosphate) grows from or crystallizes upon the surface of an intrapapillary plaque of a different chemical composition.*

All lesions on one papilla (Fig. 12). This papilla shows a number of subsurface lesions. Near the surface on the side of the papilla there is (1) a small, roughly oval area, homogeneous in appearance, composed of dense connective tissue and showing very few partly degenerated nuclei. Close by, in a similar subsurface location, is (2) a small necrotic area separated from the surface by connective tissue and covering epithelium. A short distance from this necrotic area, going toward the tip of the papilla, is (3) another area of necrosis showing a deposition of calcium salts, yet still separated from the surface of the papilla by three or four strands of connective-tissue cells and covering epithelium. Still further toward the tip of the papilla is seen (4) a small depressed area devoid of normal covering, with irregular fragments of calcium salts deposited about its base. Apparently something has been torn away from this area, carrying with it part of the calcium plaque. In no place is there any evidence of infection, or of calcium deposits in the convoluted tubules.

This section pictures a most fortunate find, for from this papilla we removed a black stone and on it have demonstrated its attached plaque (Fig. 9). It is the specimen described which was analyzed by Dr. Richards to show a calculus of pure calcium oxalate, crystallized upon a plaque of calcium carbonate and phosphate. Also, as just described, are demonstrable in this section: an undisturbed subsurface calcium plaque; an area of necrosis as yet without calcium deposition; and the earliest changes of simple fibrosis with some pycnotic nuclei. *Here is written, for those who would read, almost the entire histology and pathology of the relationship between primary tissue damage in the renal papilla, succeeding primary deposition of calcium salts, and, finally, the crystallization on such of a primary renal calculus.*

Summary. The general impressions obtained by a close study of all our specimens are: that there occurs a definite damage to the epithelial lining of the collecting tubules, and that the nearer one goes toward the tip of the papilla the more noticeable the changes are; and that there is a marked damage to the ground substance of the interstitial connective tissue and of the basement membrane of many of the collecting tubules. Here and there the ground substance is broken up and granular, and shows necrotic changes. These changes appear to be followed by the deposition of calcium salts and the gradual development of a calcium plaque. This study also reveals that in places the calcium is deposited in damaged epithelium of the collecting tubules, but the primary deposit appears to be in the basement membranes and leads to the formation of ring-like structures. No evidence of infection is seen in any of the sections presented.

PAPILLARY LESION TYPE II. INTRATUBULAR CALCIFICATION OR NEPHROCALCINOSIS

In the 227 autopsies that showed visible calcium-salt deposition in the renal papilla, 23 cases belong in a different category from the simple calcium-plaque formation just described.

Pathology has long recognized a condition wherein the terminal collecting tubules of the renal papilla have been observed choked with undissolved crystalline deposits. The uric-acid infarcts of infancy are a well known example. The "calcium infarction" of Henle is less well known; while the nephrocalcinosis of Shelling and of Albright is a third pertinent example. The part that such pathological states play in the formation of primary renal calculi has been suspected by numerous observers (Huggins, 1933, and others), and in undertaking our autopsy investigations it was one of the possibilities that we held to be most likely of positive results. In our autopsy series the small percentage of such findings, as compared to the calcium-plaque formation, has caused us to omit its description in all but one of our previous publications. When re-

porting the results of these investigations to February 15, 1937, we had observed 5 examples of this tubular "infarction" in 429 autopsies, or 1.1 per cent, as compared to the 17 per cent incidence of calcium-plaque formation in the same series. In the total series to date (1,154 autopsies) 23 (1.9 per cent) examples of this second pathological papillary lesion have been observed.

The use of the term "calcium infarction" is to be regretted, for the condition as we have observed it, both macroscopically and microscopically, would be better termed calcium inspissation of the collecting tubules.

Grossly it is quite easily distinguished, as in every instance multiple papillary involvement was the rule, with each papilla streaked with yellowish lines converging toward the tip of the papilla, at which point the cribriform membrane is heavily impregnated with visible salt deposits. Dr. Greta Hammarsten (personal communication) has correctly described it, "where it presents something of the picture of the crystallization round the tip of a pipette having stood for a long time filled with a salt solution." In 4 instances the well known uric-acid infarction was identified, and in the remaining 19, calcium salts were the offending factor. In 1 remarkable specimen the tip of each one of six papillæ (Fig. 13) supported a black secondary deposit of beginning stone formation, and in 3 other specimens small, soft, calcium phosphate stones adhered to the tip of the papilla (Fig. 14), and were definitely growing attached to such papillary tubular pathological matter. We have been able to obtain microscopic sections and to study the gross choking of each tubule with calcium-phosphate salts, to the appearance of true tubular inspissation.

In fact, this picture of gross tubular inspissation with calcium salts can be found in all varying degrees of tubular involvement, and from the drastic state above mentioned we have observed gradients of lesser involvement until, occasionally, one finds even a solitary tubule choked with calcium phosphate (Fig. 15). Twice we have observed such, situated centrally in the papilla and forming a true intrarenal calculus. A third most interesting example was sent us for study by Dr. Roderick L. Huntress of Portland, Maine, which gave every evidence of a partial though increasing obstruction to a single urinary channel. Similar isolated case reports are to be found in the literature (Crabtree, 1930; Huggins, 1933) in which varying degrees of nephrocalcinosis have been observed, both clinically and post mortem.

This calcium deposition is for the most part intratubular, and in Henle's original description he depicts it as a counterpart to intratubular uric-acid infarction of infancy, a view later corrected and modified by Lubarsch to show that the calcium salts may be also extratubular, and especially in the collagenic membrane.

Microscopic pathology. The microscopic picture, as we have generally observed it in autopsy cases, is a drastic one and in sharp contrast to the innocent appearance of the simple calcium plaque. Infection was present in 42 per cent of the autopsy cases (8 of 19), and one gained the impression that the infection was secondary and not primary. There is seen a marked fibrosis associated with degeneration and desquamation of the epithelial cells lining the collecting tubules. In all of our specimens this picture is quite generalized, and few or none of the terminal tubules escape involvement. Frequently the very tip of the papilla is necrotic, with diffuse calcium-salt deposits, and in 3 specimens in which stone was successfully sectioned it was found growing at the tip of the papilla as part of the gross picture of calcium deposition (Fig. 16). Cortex, glomeruli, and convoluted tubules show no noteworthy lesions.

That in our autopsy series this Type II lesion represents a much smaller percentage than the calcium plaque is not at all illogical, for the finding of stone has been, in relation to the finding of plaque, 1 to 3.5, which shows that practically two-thirds of the instances of plaque formation are innocent of significance in forming calculi at the time of death. Of the 19 instances of the second papillary lesion 4 showed stone present. The lower incidence of the Type II lesion suggests that its cause is based upon some infectious, dietary, metabolic, or glandular disturbances, which are comparatively rare in hospital admissions.

The hyperexcretory state. One of the five pertinent theories for the etiology of stone presupposes a disturbance in the normal colloidal mechanism of urinary excretion. The urinary colloids are recognized as holding in solution the crystalloids of the urine, and not only holding them in solution, but in a supersaturated state. It is one of the many ingenious provisions of nature whereby it rids itself, even under physiological conditions, of considerable amounts of excreted solid substances in the least possible quantity of fluid. The normal daily amount of colloid is gauged to be sufficient for the normal daily amount of crystalloid; but it is a delicate balance and is, therefore, assumed to be quite unstable, with a constant tendency to gain a more stable state by having the crystalloids fall out of

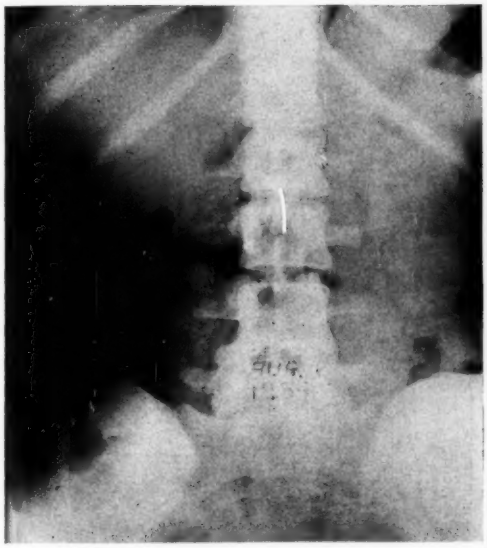

Fig. 1. Roentgenogram of August, 1934. Shadow of right renal calculus observed when searching for cause of backache on left side.

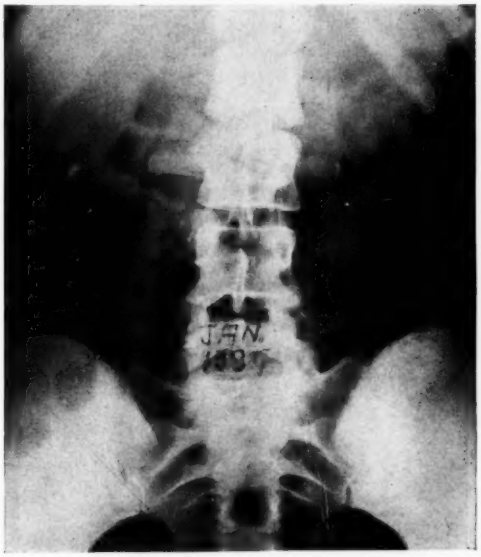

Fig. 2. Roentgenogram of January, 1937. Shadow still present and little changed.

suspension. If one disturbs this so-called colloidal balance by either increasing the crystalloid or decreasing the colloid surface area, a precipitation of crystalloids occurs and they appear in the urine as actual insoluble material.

It has been repeatedly demonstrated (Korhonen, 1936; Keyser, 1923) that the products of infection and of epithelial degeneration are recognized disturbers of the colloid mass, either by depreciating the amount of colloid or by causing coalescence with loss of surface area. Hammarsten and others have also called attention to the solvent properties of urea and the loss of such stabilization of salts when urea-splitting organisms disturb this chemical balance that exists in normal urine.

Three conditions, both experimental and clinical, come to mind in relation to the hyperexcretory state:

1. The experimental creation in animals of hyperexcretory states (Higgins, 1936; Keyser, 1923) in which, by overfeeding, there is eliminated through the kidney more crystalloid than can be held in solution by the colloid, which results in the output of a urine in such a supersaturated state that crystalloids are verging on, or actually are, precipitating therefrom.

2. One now seems able to visualize that primary renal calculi, associated with such a condition as hyperparathyroidism (recognized as a hyperexcretory state), present a similar picture and need little or nothing more to explain their etiology.

3. The nephrocalcinosis of Shelling and of Albright appears to reach exactly the same end by reason of infection with urea-splitting organisms.

The etiology of primary renal calculus in these cases seems of quite simple explanation, for here we have a disturbed chemical (or colloidal) balance and have an excreted urine supersaturated with precipitating crystalloids, and one visualizes the same picture of tubular inspissation and papillary infarction as we are describing under this title of Papillary Lesion Type II.

Simple as this seems to be to account for our need of an explanation, it still falls short in both argument and proof, and perhaps simple cystinuria can be used to aid our understanding. In the cystinuric patient we have an unquestioned hyperexcretory state, and repeatedly patients have been observed with otherwise bilateral normally functioning kidneys. Yet in such an individual *a stone may form*. Now it is known that only 2.7 per cent of the recognized cystinuric patients actually develop a renal calculus, but when it does occur, it is in but one of a pair of equally disturbed kidneys, and it arises in only one part (perhaps a minor calyx) of that one

Fig. 3. Urogram of July, 1937. Shadow of stone in inferior minor calyx of right kidney.

Fig. 4. Urogram of September, 1938. Twenty-four hours after onset of first right renal colic. The calculus is in the lower third of the right ureter and completely blocks right renal function.

kidney! Nothing could be theoretically more perfect to prove the necessity of an initiating lesion at the point of formation of such a stone. Such may be considered nature's infallible neglect by leaving behind one perfect clue to our subject.

The clinical importance and the relationship of this second type of papillary lesion to primary renal calculus becomes increasingly clear as one reviews the great mass of experimental studies wherein *hyperexcretory states* are artificially produced. By saturating an animal's economy with overwhelming doses of either a natural or an unnatural salt, an hyperexcretory state is created wherein a closely related salt appears in the urine far and above the ability of the urine to hold it in solution. Precipitation and crystallization may naturally be expected, and this papillary intratubular inspissation is the pathological picture which ensues. Likewise, in those clinical conditions wherein an abnormal hyperexcretory condition for calcium salts is recognized to exist, the relationship between such a cause and the primary renal calculus, as representing the effect, must meet through the pathological agency of such an intermediary papillary tubular lesion, and it is our hope to be able to point out just this very fact in Part III of this study, and to demonstrate why such precipitation occurs and what the necessary factors to the location of its deposition are. However, the one important fact at this point which must be constantly borne in mind is that a marked variation in the degree of the pathological condition occurs, and on this alone depends the damage to tubular epithelium, to the basement membrane, and to the interstitial supporting tissue; and, again, the varying gradients between damage, repair, and associated tissue calcification give a diversification of the clinical problem with which we are dealing.

Discussion. Our autopsy studies in man have uncovered these two types of papillary pathology, both now recognized and proved as a distinct intermediary lesion between some causal condition and the resultant crystallization which we call a primary renal calculus. This helps materially to answer those questions which until now plunged investigators into flights of theorization, each of which served to push the answer farther from us and from clinical reasoning. We now understand *how* stone starts, *where* stone starts, and *why* stone starts. We now can visualize the reason for the absence of symptoms while stone attains growth. We now can account for the element of time required for growth. And I believe

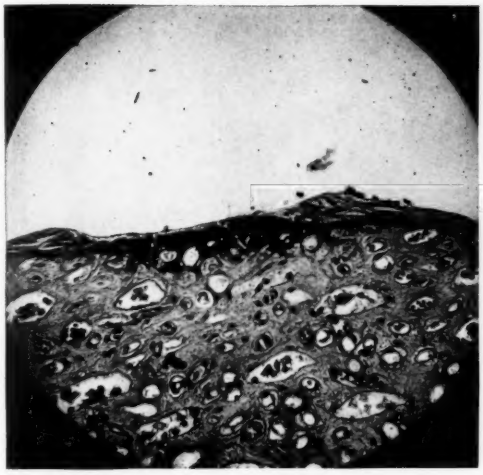

Fig. 5. Photomicrograph of a simple calcium plaque on the side of the renal papilla. Note that it is still covered by epithelium, and the absence of any evidence of infection.

Fig. 6. Papilla showing fully developed initiating lesion. To right is an enlarged photograph of a renal papilla with calcium plaques distinctly visible. To left another papilla from the same kidney, and on a plaque is seen a secondary black deposit. It is the earliest evidence of the beginning of a renal calculus.

we now can see our physiology, our pathology, and our crystallography in a more acceptable atmosphere.

The first postulate—that there had to be an initiating, or precalculus lesion—appears proved. The second postulate—that such a lesion would likely occur upon the renal papilla—likewise appears proved.

The finding of calculi composed of three different urinary salts, calcium phosphate, calcium oxalate, and uric acid, each crystallizing upon calcium plaques, and in each instance composed of salts of a different chemical composition from that of the plaque on which it grew, allows one to ascribe to this lesion—the calcium plaque—the power to be the nidus on which any urinary salt may crystallize, and to so produce a common origin that may account for the known diversity of the chemical composition of urinary calculi.

Our Type II papillary lesion has not only been of rarer occurrence, but has also caused us greater trouble to rectify its pathology with both cause and effect. That primary renal calculi can arise therefrom we can vouch for, as we have observed 4 such cases. That it is more commonly associated in clinical cases with only the deposition of calcium phosphate seems true likewise, and this places it in the clinical group associated with urea-splitting infection, hyperparathyroidism, and hypovitaminosis A. Why we believe that these three causative conditions, though possible, are quite in the minority, we hope to show later when studying the broad clinical subject of primary renal calculus.

The result of this research upon human autopsy material, while explaining the origin of primary renal calculi by demonstrating the morbid pathology of the human renal papilla, left unanswered the question as to why such papillary pathology occurred, and led us directly to institute further studies, now of an experimental nature in animals, to try to prove if any of the current theories in regard to the etiology of stone produced the types of papillary pathology with which we were familiar from our studies in man.

Part III. Research on the Pathology of the Renal Papilla: Papillary Calcification in Experimental Animals

Thus having proved that two types of initiating lesions have been found and that, in specific instances, they were directly related to the origin and growth of primary renal calculi, our interest next lay in trying to understand their cause and perhaps their relationship to the five theories intimately associated in clinical and experimental studies of the stone problem. The five pertinent theories for the causation of renal calculi, (*a*) stasis, (*b*) infection, (*c*) avitaminosis, (*d*) colloidal imbalance, and (*e*) parathyroid hyperfunction, were weighed against the evidence at hand. Stasis was again ruled out as playing no demonstrable part in the clinical studies of primary renal calculus in which we were interested. Colloidal chemistry, though fascinating in its theoretical possibilities, seemed most refractory both

as to a causal relationship to the lesion and to experimental investigation, though certain features in which it may properly play an important part have been referred to under the "hyperexcretory state." It is to be assumed that colloidal chemistry, and the so-called colloidal balance, probably play a dominant rôle in the determination of which urinary salt shall crystallize and form the stone. The remaining three, each of which has developed ardent advocates and has amassed an enormous literature, gave the greatest promise of being related to the deposition of calcium salts as seen in our papillary pathology, and each was subjected to experimental study in a series of problems now to be presented and discussed.

RESEARCH STUDIES ON THE RÔLE OF INFECTION

In discussing the rôle that infection plays in the etiology of renal calculus, we enter a phase of the question in which two distinct schools exist: one positive that it is the hidden answer and cause; the other equally adamant that it is not. In order to view the subject clearly, let us strip it of its complicating features and states. Let us put aside those cases of calculus pyonephrosis in which pathology has existed so long, or has progressed so far, that the characteristics of onset are obliterated. Again let us set aside those wretched cases of chronic pyelonephritis with persistent alkaline urine and phosphatic deposits or incrustations, and with them the rapidly recurrent postoperative cases, most of which belong in the same category. I should like also to exclude the cases of long-standing calculus disease, judged by either history or size of stone, in which the entrance of infection becomes quite an unknown factor. All of which, again, is an attempt to limit this particular study to the primary renal calculus of recent acquirement, and to the experimental studies of recent years in which attempts were made to produce stone by means of bacterial agents.

Fig. 7. Photograph showing a tiny calculus upon a renal papilla. Calcium plaques on other papillæ. This stone was of calcium phosphate.

Fig. 8. Photomicrograph of section through specimen in Figure 7. The calculus (x) has been successfully decalcified and sectioned. It is distinctly attached to its plaque (y) and growing only therefrom. By differentiating stains the calculus has been proved to be calcium phosphate and the plaque a different salt of calcium, probably the carbonate.

There is little doubt that our kidneys are being bombarded more or less constantly by blood-borne bacteria, but the same is true of our other body organs, and we must realize that such bombardment is sustained with competent resistance and without tissue injury. Today we no longer believe that organisms pass innocently through the kidney, or that there is such a thing as a passive, or innocent, bacilluria. Again, we must also realize the now well accepted fact that, in the absence of obstruction and stasis, it is practically impossible to have a chronic infection of the human renal pelvis. So with these weapons the

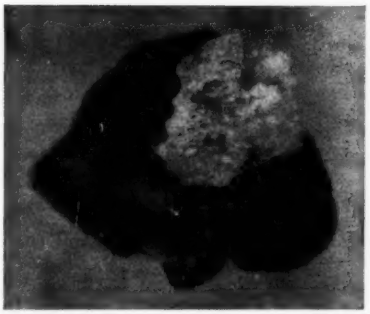

Fig. 9. Calculus which was found attached to a renal papilla and gently removed. The stone weighs 5.5 mgm. and measures 3 mm. across. The black portion has been analyzed and proved to be composed of calcium oxalate. The white portion represents the torn-out calcium plaque upon which the stone crystallized, and is composed of calcium carbonate and phosphate.

anti-infectionists arm themselves and stand ready to meet the attack of the large host who see in bacteria certain characteristics that seem to fit where certain links are missing in the chain of evidence to prove that the etiology of stone is of infectious origin. The evidences (1) that infection disturbs colloidal balance (Korhonen, 1936; Keyser, 1923); (2) that infection produces epithelial or bacterial clumps, upon which crystallization may occur (Eisenstaedt, 1931; Berke, 1937); (3) that infection may cause papillitis, even to ulceration (Aschoff, 1913; Pannett, 1915); (4) that bacteria have been demonstrated in, and cultured from, the center of calculi (Hryntschak, 1935; Hellstrom, 1936); and (5) that the presence of urea-splitting organisms results in calcium-phosphate precipitation and incrustation (Hellstrom, 1929; Grossman, 1933; Eisenstaedt, 1931; and others) are all arguments to show the close relationship between an infectious state and the occurrence of renal stone. Likewise, one must mention, only to exclude, those frequent reports of the association of chronic infectious conditions and prolonged recumbency and immobility (Watson-Jones and Roberts, 1934; Lee-Brown and Earlam, 1933; Goldstein and Abeshouse, 1935; Costello, 1932; Joly, 1929; Higgins and Schlumberger, 1937; and many others), in which, however, the unnatural relationship of infection and postural stasis undoubtedly develops a predisposing cause that is quite aside for the moment from our problem of the primary renal calculus. From 1922 to 1925 Rosenow and Meisser presented extremely convincing evidence, when they performed their oft-quoted experiments on dogs, by implanting streptococci obtained from the urine of a patient with typical attacks of renal colic due to calculus in the pulp cavity of the teeth, and having 5 of their 6 dogs develop renal stones. In fact, in a larger series of dogs so studied, 87 per cent (30 of 34 dogs) "revealed either calculi or localized lesions in the medulla, or both," when streptococci suspected of having specific renal affinity were implanted in dogs' teeth (Rosenow, 1925). Such a marked specificity of organisms is not generally recognized in medicine, and Hryntschak (1935), a strong advocate of the infectious origin of stone, repeated this work and reported completely negative results. Certain it is that stasis plays no part in Rosenow's experiments, and the lesions of the medulla that he describes suggest certain observations which we have made and which are to be reported further on. It is surprising that Rosenow's simple method of producing focal infections at will has been so neglected, and one is permitted the thought that it has been used and unreported because of indifferent results. It is worthy of greater use and application. One is tempted, however, to give more weight to Rosenow's observations than has been credited to date, and though his enthusiasm may have carried his ideas too far afield, yet I believe proof will be forthcoming that will substantiate some of his observations relating chronic focal infection with the origin of stone.

Fig. 10. Photomicrograph at edge of specimen shown in Figures 7 and 8. It shows the crystallization lifting the edge of the plaque from its papillary attachment, and it is thusly that a stone gains freedom.

Fig. 10a. Roentgenogram of pure uric-acid calculus with the inclusion of an x-ray-positive nucleus or nidus. This nucleus has been analyzed and proved to be composed of calcium salts. This is taken as proof that the uric-acid crystallization took place upon and around this primary nidus, which must have been deposited in the renal papilla as a calcium plaque.

If primary renal calculus is the product of an infectious agent, it would seem that when such a stone blocks the ureter and causes intense colic from pelvic distention, the resultant trauma to the kidney (at times reaching a degree where renal function ceases and stagnation exists) creates the most perfect stage-setting for a rapid dissemination of the infectious process. For this reason I have taken 75 such cases, observed practically consecutively, in which open ureterolithotomy was necessarily performed, and in which in each instance the pelvic urine was cultured at the

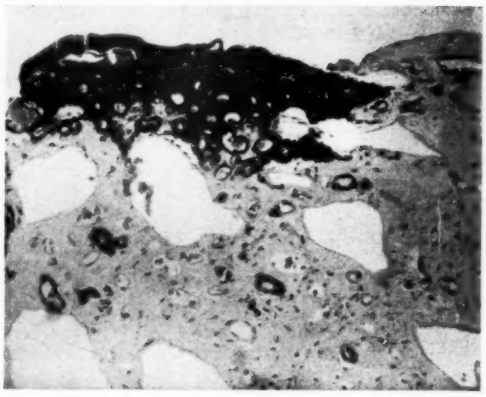

Fig. 11. Photomicrograph of fully developed initiating lesion shown in Figure 6. Here the epithelial covering of the calcium plaque has gone, probably from pressure of the increasing deposit, and the plaque lies raw and bathed in calycine urine. The wrinkled outer layer is of different color and character and is distinctly laminated. It is unquestionably a secondary deposit and of different chemical character. It is the earliest evidence of the beginning of a primary renal calculus.

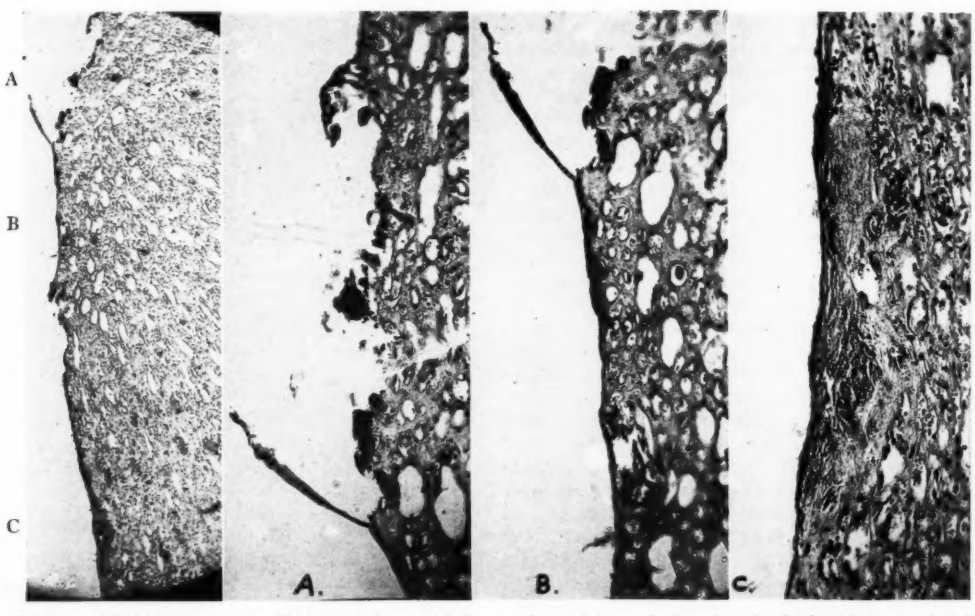

Fig. 12. All lesions on one papilla and section. At left is low power photomicrograph showing at A the area from which the calculus in Figure 9 was removed, at B a subsurface calcium-salt deposit or beginning plaque, and at C an area of ischemia and necrosis. Succeeding pictures are these three areas under higher magnification.

Fig. 13. Typical papillæ (6) from one kidney showing Papillary Lesion Type II, "calcium infarction," or nephrocalcinosis. The interesting point is that each papilla has a secondary black deposit on its tip, reproducing in this Type II lesion what we have already illustrated in Figure 6 in the Type I lesion, i.e., the earliest evidence of beginning crystallization of a primary renal calculus.

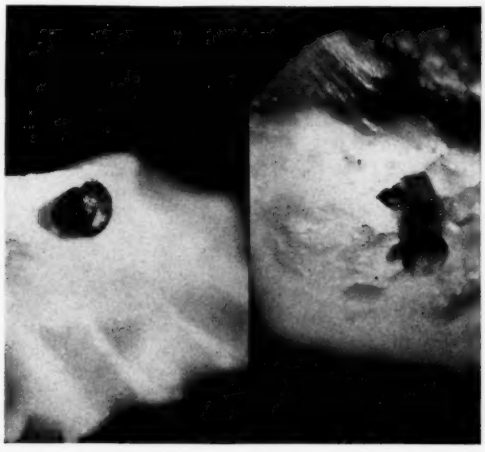

Fig. 14. Photomicrographs (low power) of the tips of two papillæ illustrating Type II lesion. Each is snowy white from "calcium infarction," and on each is growing a primary renal calculus.

operation. These 75 cases, almost without exception, represent instances wherein the evidences and symptoms of the existence of stone were of short duration. Almost every one was suffering from his or her primary colic, and in no case were stones of large size (over 2 cm.) present. They were essentially cases of primary renal calculi in their first attack of ureteral colic, in which urography proved the stone too large and too high to expect further ureteral passage. I believe this to be a more accurate method than culture by cystoscopic catheterization, and in fact the great majority of these cases were not instrumented at all. In 36 patients, or 48 per cent, the pelvic-urine cultures were sterile; 31 patients had single and 5 had multiple calculi. In 39 patients, or 52 per cent, cultures of the pelvic-urine proved infection to be present; 34 patients had single stones and 5 multiple.

This percentage of 52 to 48 is certainly not conclusive, but under these ideal clinical conditions the 48 per cent of sterile pelves is of greater significance in proving that infection does not play an essential rôle than the 52 per cent that were found to harbor an organism. Moreover, the organisms found present in those that were infected do not coincide with the expectations of the advocates of an infectious origin for stone. The organisms found present were of 15 different identities and 6 different combinations of these, the staphylococcus albus 15 times, streptococcus 8 times, bacillus coli communis 8 times, being the most frequent offenders. This makes 38.5 per cent proved of association with the staphylococcus albus, which is far from Hellstrom's 66 per cent, which he broadens to 75 per cent, and which allows him to state that "the essential cause of the formation of these concrements is undoubtedly the staphylococcic infection." In fact, Hellstrom meets with difficulties in interpreting his own observations, for he says in evaluating "the connection between staphylococcuria and stone formation, examination of the ureteral urine is of great significance. This has been done in 67 cases." Then after an excellent tabulation he states, "In no less than 23 cases with unilateral stone, or almost one-third of the material so studied, there have also been staphylococci on the side where there was no stone. This suggests that the staphylococci are not the only determining factors in stone formation, but that there must be in addition other, especially local, conditions of the kidney and urinary passages." Also in 8 of his 67 cases (12 per cent) ureteral culture was sterile on the stone side, and in 3 further cases (4.5 per cent) no staphylococci could be demonstrated, but bacilli coli were present.

One does not wish to quote Koch's stipulations, but the large hiatus that exists between theory and fact has not been satisfactorily bridged by the

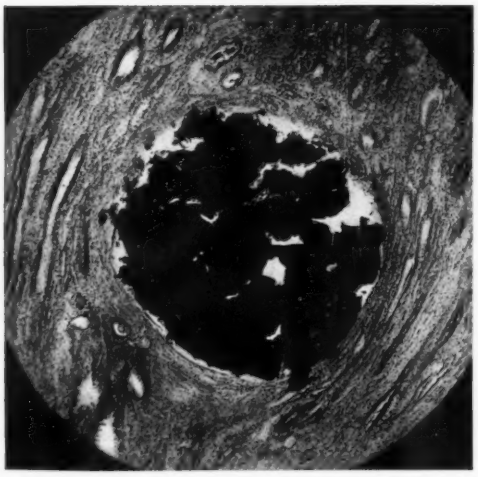

Fig. 15. Illustration of a solitary tubule packed with calcium phosphate. This was found in the middle of the papilla and was probably purely obstructive. (Von Kossa stain.) (Specimen from Dr. Roderick L. Huntress, *vide loc.*)

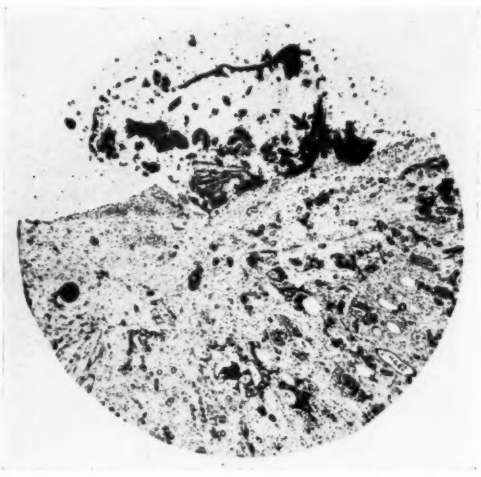

Fig. 16. Photomicrograph of the tip of a papilla illustrating massive tubular inspissation with calcium phosphate (von Kossa stain), and supporting a primary renal calculus of the same material. Decalcification for microscopic section cutting has dissolved some of the calcium phosphate. This is from specimen shown in Figure 14.

proponents of this theory, who try to make the etiology of stone totally dependent on local infection.

Toxin studies. The material from our autopsy studies, which demonstrated our calcium-plaque lesion, consistently failed to show (excepting 9 of 227 cases) the slightest evidence of infectious reaction in association with such lesions; there were no exudate, no round-cell infiltration, no necrosis, and no organisms. In fact, almost uniformly the evidence of infection was particularly conspicuous by its total absence, and focal infection of the papilla as a cause of such calcification was quite out of the question. From our studies it simply cannot be included. *The effect of bacterial toxin, however, was quite another matter,* and as the lesion gave every evidence of being a calcium deposition in response to some form of damage to the collecting tubules, there was the possibility that the concentration of some such toxic material at this point could be the primary cause. In the laboratories of the Abington Memorial Hospital a staphylococcus toxin was elaborated, and we injected it into rabbits in a small series of experiments. This toxin proved to be too potent to work with accurately, and the animals died promptly after the injection of 0.2 c.cm.; so a toxoid was prepared by the addition of 0.2 per cent of formaldehyde and incubation at 39°C. from twenty-four to forty-eight hours. The experiments consisted of the intravenous injection of 5 c.cm. of this toxoid, to be followed by simultaneous collection of blood and urine at frequent intervals over the following three or four hours for the titration of this toxoid content. It was to be assumed that the concentration of the toxoid in the glomerular filtrate would be the equal of that in the plasma and that somewhere along the renal tubules concentration of the toxic material would occur, and we wished to find out if this could be observed.

In an experiment with a rabbit weighing 2,700 gm., in which 5 c.cm. of staphylococcus toxoid of L.B. 0.01 was injected intravenously, subsequent titrations proved that at the highest reading this toxoid was present in the urine in a concentration five times greater than in the blood stream at its maximum concentration at five and ten minutes after injection. This rabbit secreted 0.13 c.cm. of urine per minute.

In a second similar experiment a rabbit, weighing 1,940 gm., was given an intravenous injection of 5 c.cm. of the same toxoid of L.B. 0.02. This toxoid was recovered from the urine in a concentration sixty times greater than that in the blood stream at its point of maximum concentration. This rabbit secreted 0.02 c.cm. of urine per minute.

These examples, together with others, from our series of 10 similar experiments, seem definitely

Fig. 17. The collecting tubules in a rabbit's kidney after the administration of a stable streptococcus hemolysin leucocidin. The damage to the tubular epithelium is marked.

Fig. 18. The tip of the papilla of a rabbit's kidney following the administration of a stable streptococcus hemolysin leucocidin, showing very advanced damage to all tubular structures.

to prove that the kidney can and does concentrate this toxic material from two and a half to sixty times the blood-stream content. The tabulation and complete protocols of this experimental work have been reported by Dr. Ezra Casman (1937).

This work has been repeated since its first publication by Dr. Casman, and in our "Studies on the Pathology of the Renal Papilla" (1937), and similar results have been obtained. In 6 rabbits subcutaneous injections were tried, but failed to give evidence of renal excretion in recognizable amounts.

Through the courtesy of Dr. Stuart Mudd, Professor of Bacteriology, University of Pennsylvania, we were supplied with some of his stable streptococcus hemolysin leucocidin; we desired to use it because it is a haptin and does not give rise to the formation of antibodies when injected into animals. It was injected into a small series of rabbits, as we wished to study histologically the effect upon the tubules of the kidney, and the following protocols are characteristic:

Rabbit 8, weighing 1,308 gm., was given 1 c.cm. of a 1:500 dilution on each of three consecutive days. Death followed the third injection. Grossly the kidneys showed no noteworthy lesions. Microscopically there was cloudy swelling of the epithelium of the convoluted tubules and albuminous exudate into Bowman's capsule. The collecting tubules showed marked degenerative changes: the lining epithelial cells were necrotic and in many places desquamated; in other places the basement connective tissue was damaged. At the very tip of the papilla was an area of necrosis.

Rabbit 6, weighing 1,370 gm., was given eleven daily injections of 1 c.cm. of the same preparation in a 1:2,500 dilution. The only lesions observed were microscopic and showed necrosis of a few cells in a number of the collecting tubules, with no lesions in the glomeruli or in the convoluted tubules.

All the control rabbits were entirely normal.

Such kidneys present conclusive evidence that damage has been suffered by the epithelium of the renal tubules, and, though cloudy swelling is present in the convoluted tubules when high concentrations have been given, the greatest damage of all is in the terminal collecting tubules, in parts of which even epithelial exfoliation can be observed (Figs. 17 and 18).

These experiments are of the utmost interest, and seem to prove three very important facts: (1) *that the kidney does excrete bacterial toxins;* (2) *that the kidney does concentrate bacterial toxins while excreting them; and* (3) *that the elimination of a streptococcus toxin through the kidney can cause definite localized epithelial damage, which is most marked in the walls of the collecting tubules.*

Naturally, the concentration of any toxin in the urine varies inversely with the amount of urine excreted, and this fact alone carries attractive therapeutic implications.

Relating this papillary pathology to the elimination of bacterial toxins caused us to wish to determine the result from the excessive administration of a simple chemical toxin, realizing full well—following Richard's masterly work on the selective activity of the various parts of the renal tubule—that the location of insult may vary. A small group of rats were given uranyl acetate, and the observations in 2 of them will suffice to illustrate the result:

Rat 47 received at two-day intervals 15 mgm. of uranyl acetate intramuscularly. Seven days after the first dose, and three days after the last dose, it was sacrificed. Microscopic study showed the epithelium of the convoluted tubules to be necrotic; the loops of Henle showed no noteworthy changes, except that 2 or 3 of them contained some intratubular calcium salts; the collecting tubules of the papilla contained casts and showed marked damage to the lining epithelium with desquamation, but no calcium deposits.

Rat 48 received the same dosage as Rat 47, but was not sacrificed until ninety days after the last injection. The epithelium of most of the convoluted tubules had regenerated, though a great many tubules showed a lack of regeneration of the lining epithelium and were filled with irregular calcium salt deposits. The epithelial lining of the collecting tubules was regular, though many cells contained albuminous material. The tip of the papilla showed a marked increase of the intertubular connective tissue.

Assuming that both rats responded equally to the injections of uranyl acetate, the time element seems to be the only explanation of the difference in the pathological picture in the kidneys of the 2. Rat 47, killed three days after the last dose, showed extensive necrosis of the convoluted tubules, and apparently not enough time had elapsed for the deposition of calcium salts. In the kidneys of Rat 48, killed ninety days after the last dose, there were found extensive deposits of calcium salts in the necrotic epithelium of the convoluted tubules.

Discussion. From our observations, both gross and microscopic, on our autopsy material we have not been able to associate the initiating lesions of primary renal calculus with generalized or localized infection of the kidney proper or of the renal pelvis. This being an observed fact, it forces the unavoidable conclusion that such cannot be of further interest to us in searching for the etiology of renal calculus. But the relationship of infection to stone is too intimately associated in clinical medicine to be brushed aside so easily, and for this reason the experiments with bacterial and chemical toxins were performed. We have described the observation that each of these agents has caused localized damage to the renal tubules and their lining epithelium. As might be expected, this damage varies with the concentration of the toxin, and likewise the reparative process is expressed in varying degrees of tissue regeneration. Only in the chemical-poison studies have we seen calcium-salt deposition in the tubules; but the bacterial toxin has been hard to control, though we can point to the similarity of cellular damage and safely argue by analogy that reparation would follow similar lines.

I believe it safe to conclude, having demonstrated the localized damage to tubular structures by the administration of bacterial and also chemical toxins, that either the complete reparative process that follows an acute renal insult of such toxic nature, or the kidney's reaction to a low grade, but oft-repeated, toxic insult can be directly associated with tubular and intertubular calcium deposition, similar in every way to that which we have observed in man and described. The frequency and the degree of insult will account for the variations in the observed lesions; and in all cases calcium deposition is to be recognized as a natural sequel to tissue insult and is comparable to calcification as seen elsewhere in the body under similar circumstances.

RESEARCH STUDIES ON THE RÔLE OF VITAMIN A DEFICIENCY

This ground has already been extensively covered, but it was felt that our approach to it would be slightly different. In the first place we were interested to see if such hypovitaminosis could produce true calcium plaques as found in man. Secondly, we wished to study less drastic pictures of hypovitaminosis than those reported in most experimental work and, in so doing, to create conditions more nearly simulating possible clinical states. And finally, we wished to study the locations in which calcium is deposited in the kidney as possibly bearing upon the initiating lesion.

It may be fairly stated that under this heading is now grouped the entire rôle of diet in stone formation. That a deficiency in Vitamin A is the prime requisite is also well recognized, and that such a deficiency creates a disturbance in the normal calcium-phosphorus ratio and produces marked changes in the epithelial lining of the urinary tract seems equally well established. The original work of Osborne and Mendel (1917), the feeding experiments of Van Leersum (1927), McCarrison (1931), Hou (1936), Higgins (1933), Wolbach (1937), Grossman (1933) and numerous others point to the unquestioned fact that hypo-

vitaminosis A (Vitamin A deficiency) is associated with specific changes throughout the body, and that no tissue suffers more severely than the epithelium lining the urinary tract (McCarrison). These changes consist first of areas of epithelial proliferation, seen especially in our specimens in the papillary-calycine angles, to be followed by degeneration and desquamation and, later, by keratinization. Certain authors have likewise associated Vitamin D with this picture (Wolbach, 1937; Bernheim, 1933; Gray, 1935; Livermore and Prather, 1933; Saiki, 1933) because of its well known effect on calcium and phosphorus metabolism, but its part seems limited to the observation that Vitamin D increases the incidence of urinary concretions when added to a Vitamin-A-deficiency diet in experimental studies.

Discussion of this theory must be confined to those factors known to be truly relevant. First, it is to be pointed out that the calculi which form under conditions of hypovitaminosis A are consistently made of one salt from those elements known to have their normal ratios disturbed; that is, calcium phosphate. Stones of uric acid, urates, or even calcium oxalate, do not participate in the picture at all. Experimentally, if the phosphorus is radically diminished in the diet, calcium carbonate can be made to crystallize, and occasionally calcium and magnesium phosphate have been observed (Keyser, 1938; Higgins, 1935 and 1937). Second, the alkaline urine is to be especially noted; it appears promptly after starting the diet and is of marked degree, and with it occurs a high incidence of urinary infection in the experimental animals. In most studies the incidence of calculus formation is practically equal to that of urinary infection, though Gray (1936) found 5 of 6 such renal calculi sterile, but remarks that the incidence of calculus increases with the incidence of infection. Higgins (1935) reports the interesting observation that acidification of the urine by drugs decreases the incidence of stone in animals on Vitamin-A-deficiency diets, which suggests the causal relationship of a persistent phosphaturia in these animals. Third, it is assumed that the earliest formation of crystalline material (calculus) is about desquamated epithelial cells acting as a nidus, and it is true that vesical stone is much more frequent (88 per cent) than renal stone (42 per cent), though neither makes its appearance until marked changes in the epithelium have developed.

In a previous paper (Randall, Eiman, and Leberman, 1937) we published the dietary techniques used, and the rat groups with their results as seen in our experimental studies to that date.[1] The material was then incomplete, and some of the animals had not then been sacrificed. The first series consisted of 112 rats of Wistar Institute breed, and it is perhaps of pertinent significance that in the past these rats have shown themselves particularly resistant to the effects commonly caused by Vitamin-A-deficient diets. This is attributed to the high vitamin diet which they have been fed and to the storage of vitamins in their systems. As such they were ideal for our experiment, since their vitamin loss is gradual and the experiment follows a more typical clinical and chronic course. A second series, composed of 25 rats, have been added to the study. These were all the ordinary white laboratory rats, and each group was given Higgins' (1933) Vitamin-A-deficiency diet. In all, twenty different groups of rats were used, varying from 5 to 12 rats in a group, varying as to age, varying as to litter mates, and varying under five different dietary regimes. In our report in 1937 only about 60 per cent of the experimental animals had been sacrificed and, together with those which had died, were subjected to an autopsy, and studied. This was because we were killing the animals at specified intervals of time in order to observe both the early and the late lesions. These rats subsisted on this Vitamin-A-deficient diet for from forty-eight to one hundred and ninety-five days (an average of 108.2 days). We can now report on the entire study.

Pathology. It is to be emphasized that these rats were handled so as to make the experiment simulate as nearly as possible a clinical human group on a mild degree of Vitamin A deficiency, carrying it over as long a period of time as possible, and striving to produce not too drastic a state of hypovitaminosis. The great majority of the rats gained in weight during the first six or seven weeks of the study, though showing characteristic signs of Vitamin A deficiency—weakness, xerophthalmia, and loss of hair. Later cachexia became progressively marked, and often a little cod liver oil was given to distinct advantage. Eighty-five rats in all lived more than one hundred and thirty days, and practically only in these were kidney changes at all consistent.

Five rats developed bladder calculi, their autopsy studies being made on the one hundred and second, one hundred and twelfth, one hundred and nineteenth, one hundred and nineteenth, and one hundred and fortieth days of their experimental diet, and it is to be noted that the kidneys in each of these rats were studied es-

[1]This study was made possible by the courtesy and co-operation of the Wistar Institute of Anatomy, University of Pennsylvania.

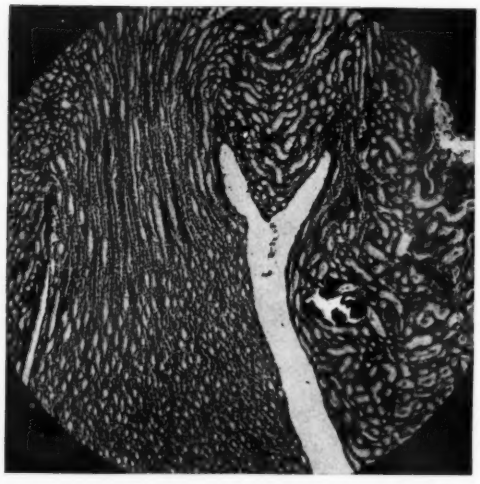

Fig. 19. Earliest evidence of calcium-salt deposition in rats on a Vitmain-A-deficient diet. This is in the calycine wall high in the calycine fornix, and it is subsurface. Further down this calycine wall is found epithelial proliferation leading to keratinization.

pecially and considered negative for any evidence of calcium deposition.

Microscopically the kidneys of rats living more than one hundred and thirty days began to show increasingly marked venous engorgement, at times so extreme as to present engorgement of all the small renal vessels, at times true hemorrhage into the peripelvic tissues, and once there was observed rupture and hemorrhage into the pelvis at the papillary-calycine fornix.

From one hundred and forty days onward the characteristic keratinization of the epithelial lining of the pelvis became increasingly evident. It generally appeared first on the calycine wall high in the fornix, and was unassociated with any evidence of infection or actual tissue degeneration. Still older rats showed in 4 specimens a true *aseptic* ulceration, three times of the calycine wall and once on the papilla, but definitely without evidence of bacterial invasion. It was perfectly evident that the epithelium lining the renal tubules suffered in the progressive avitaminosis. In the convoluted tubules the lining epithelial cells were seen to be swollen, ragged, and in varying stages of degeneration. The collecting tubules showed enlarged lumina, with cells in differing stages of degeneration. Throughout all sections were seen hemosiderin deposits and congested vessels, giving evidence of long-standing vascular engorgement, even to microscopic hemorrhages. The damage seemed to be most marked at the base of the pyramid where collecting tubules begin and convoluted tubules end, and where in the rat the line is well demarcated and the interstitial supporting tissue normally increases in amount from this point throughout the pyramid. The maximum damage was at this point, but continued on down the collecting tubules to the tip of the papilla. Throughout this area could be seen an increase in young connective-tissue cells, congested vessels, small hemorrhages, and hemosiderin deposits. One could find vascular endothelial cells which likewise showed evidences of having suffered injury, even to the capillaries in some of the glomeruli.

Calcium-salt deposition was most carefully studied. It first appeared in rats sacrificed at one hundred and forty days (on Higgins' Vitamin-A-deficient diet), became increasingly evident in those studied after one hundred and fifty-four days, and in all rats sacrificed after from one hundred and sixty to one hundred and ninety-five days increasing amounts of calcium-salt deposition were present.

The location of the calcium-salt deposition was extremely interesting. It first made its appearance high in the calycine fornix, associated perhaps with early epithelial changes, but distinctly under the lining epithelial coat (Fig. 19). Subsequent deposits occurred in the convoluted tubules in the region at the base of the papilla, and apparently where the papillary-medullary junction changes the entire structure of the tubules with increasing connective-tissue stroma. In those rats longest in the condition of hypovitaminosis the tubules of the papilla became choked with inspissated intratubular calcium salts (Fig. 20). In some specimens, in which epithelial damage was marked, calcium salts were found in the base membrane, and in places the supporting intertubular tissue was found invaded (Fig. 21). But nowhere did we observe a true calcium-plaque formation, nor did any rat develop a true renal calculus.

Discussion. Our studies with hypovitaminosis A have failed to reproduce any lesion even suggestive of the papillary lesion Type I, i.e., the calcium plaque.

All the microscopic studies have shown that though the earliest evidences of calcium-salt deposition are in the region of the base of the papilla and in the papillary-calycine fornix, they are at the same time essentially intratubular deposits. A later stage shows an increasing majority of the collecting tubules of the papilla heavy with calcium-salt deposits, and a beginning deposition

in the tubules of the medulla and cortex. The final stage is reached when intraglomerular calcium is observed.

This points clearly to the conclusion that when primary renal calculus occurs as the result of Vitamin A deficiency, it must have its origin from the papillary lesion Type II and is definitely related to the nephrocalcinosis of a hyperexcretory state. We are rather prone to concur with the conclusions of the Council on Pharmacy and Chemistry of the A. M. A. (1935) that "A-avitaminosis does not appear to play a significant part clinically in urinary lithiasis." This agrees with both our autopsy studies and these rat experiments, for our rats on gradual and prolonged hypovitaminosis A did not develop primary renal stone, did not develop calcium plaque, and only produced the Type II papillary pathology that is quite infrequent (1.9 per cent) in the autopsy studies. There can be little doubt that under drastic experimental conditions calcium-salt deposits occur, and that stone can be made to develop; but in our rats on prolonged, slow hypovitaminosis the picture is one of definite renal engorgement and epithelial damage, both to the pelvic wall where keratinization develops and to the tubule lining cells where degenerative changes and repairs are observed. Tubular deposits of calcium salts follow and may be quite extensive, and finally calcification of tubule walls and scattered interstitial deposits appear.

Fig. 20. Rat's renal papilla in late stage of Vitamin-A deficiency, illustrating tubular damage and marked inspissation of calcium phosphate.

RESEARCH STUDIES ON THE RÔLE OF HYPERPARATHYROIDISM

Known to medicine for many years as von Recklinghausen's disease, osteitis fibrosa cystica has been recognized only within the past decade as due to disturbed parathyroid function. First suggested by Askanazy in 1904, the association has been clearly established through the classical observations of Mandl (1926), DuBois et al. (1930), and Ballin (1931), to be still further substantiated by the brilliant studies of Aub, Bauer, and Albright and their co-workers in Boston (1934).

The basic observations prove that hyperparathyroidism is usually due to a functioning adenoma of the parathyroid glands. In some cases there appears only a hyperplasia of the parathyroid tissue. The result in either case is an increased production of the parathyroid hormone and an associated disorder in the metabolism of calcium and phosphorus. This disturbance becomes clinically recognized by an increase in the serum calcium level, or hypercalcemia, a decreased serum phosphorus level, or hypophosphatemia, and an increased excretion of both elements in the urine, i.e., hypercalcinuria and hyperphosphaturia. There occurs what MacCallum many years ago termed a "calcium diabetes," though today some consider hyperparathyroidism as a generic term for a disorder of the calcium-phosphorus metabolism, the diagnostic criterion of which is basically a hypophosphatemia with a hyperphosphaturia. Albright, Bauer, Claflin, and Cockrill (1932) spoke of primary hyperparathyroidism as a disorder based upon an idiopathic parathyroid adenoma, and secondary hyperparathyroidism as a functional hyperplasia secondary to the subsaturation group of bone diseases, with the urine in either case becoming supersaturated with calcium phosphate. Albright pointed out—and it should not be lost sight of—that if a calculus "is the result of hyperparathyroidism, it should contain a large amount of calcium and phosphorus." In the series reported by Albright et al. renal stone occurred in 28 per cent of the cases of proved hyperpara-

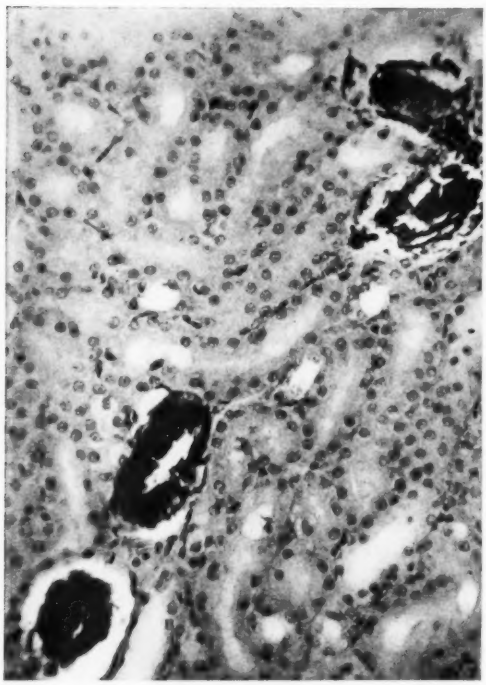

Fig. 21. Terminal stage of calcium deposition in Vitamin-A-deficient rat. All tubular epithelium damaged and calcium phosphate deposited into collagenous membrane.

thyroidism; i.e., 23 times in the series of 83 cases which he collected from the world's literature. This figure varies in the literature from 18 per cent, as reported by Rankin (1935), to 61 per cent, as reported by Colby (1934) from the Massachusetts General series. Looked at from the broader field of the actual occurrence of renal stone, Barney and Mintz (1936) could attribute but 5 per cent of 300 cases of renal lithiasis as due to proved hyperparathyroidism, and the wide variation in these figures is further disturbed by a recent study reported by Griffin, Osterberg, and Braasch (1938) in which during a review of 1,206 cases of renal lithiasis, only 2 (0.18 per cent) could be proved as due to hyperparathyroidism, and these authors urge that even when a high value of blood calcium or phosphatase is present, patients with urinary calculi "should undergo a thorough investigation for some other co-existent pathologic condition than hyperparathyroidism."

The rapid strides which many studies have made in this field have undoubtedly uncovered a very pertinent relationship between the occurrence of primary renal calculus and the hyperfunction of the parathyroid glands. Quick and Hunsberger (1931), and Wilder and Howell (1936) believe they have shown a relationship between Vitamin D deficiency and parathyroid hyperplasia, and that under normal conditions the maintenance of the normal calcium level in the blood is under the dual control of Vitamin D and the parathyroids, the former aiding in the absorption of calcium from the intestinal tract, the latter in mobilizing the element from osseous tissue.

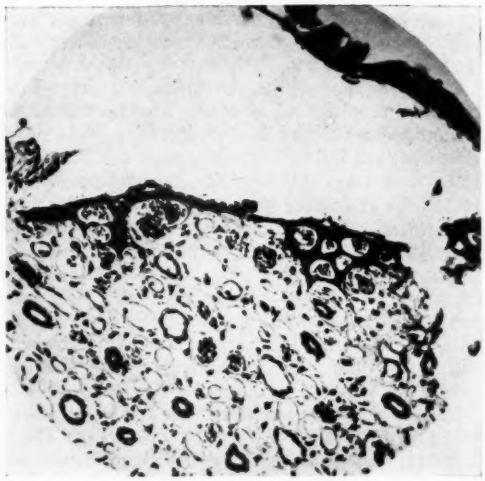

Fig. 22. Calcium plaque in wall of renal papilla of dog (No. 97) after 165 days of parathyroid hormone administration. Rather diffuse calcium-salt deposition throughout papilla.

We wished to trace in animals, given parathyroid hormone to a point of hyperparathyroidism, the relationship existing between this condition and the possible occurrence and character of initiating lesions in the renal papilla for stone. Mandl and Uebelhoer (1933) had followed this idea on male guinea pigs, administering subcutaneously 10 units daily for four weeks, and creating daily a temporary urinary stasis by elastic bands on the penis. At autopsy all animals had dilated bladders; 1 animal had dilated ureters; 3 animals had crystalline deposits in the renal pelvis; and all animals had calcium cylinders in the renal tubules and some atrophy of the lining epithelium. Huepner (1927), Jaffe et al. (1931), and Moehlig et al. (1935) had all observed renal calcification on the administration of a parathyroid extract. Cantarow, Stewart, and Housel (1938) had also followed this line of thought, using 6 adult dogs, though their efforts were to

Fig. 23. Photomicrograph of calcium plaque on renal papilla of dog after parathyroid hormone administration. Note scattered tubular calcium salts and damage to tubular epithelium.

create an acute condition, and large doses (2,700 to 3,500 units) were administered over a period of seventy-two hours. They observed swollen and edematous kidneys, and degenerated tubular epithelium which was necrotic in parts. There were extensive deposits of calcium "chiefly in the cells of Henle and the convoluted tubules."

We were desirous, in our approach to the experiment, to simulate a slow, chronic effect, and for the purpose were supplied by Eli Lilly & Company with their preparation, Parathormone. We chose dogs as the best experimental animal. The details of our first series were published in 1937, and may be summarized as follows:

Fifteen dogs were used, and daily administrations were given subcutaneously; at times the

Fig. 24. Drastic tubular damage and calcium-salt deposition, both intratubular and intertubular, after parathyroid hormone administration in a dog.

doses were as high as 500 units. Weekly blood chemistry studies were made, and when possible, urine estimations for the calcium output were recorded. When the animals appeared to be losing ground, a rest period of from seven to ten days was allowed, and almost all received some viosterol in their daily food at selected intervals. This regimen was kept up from four to six months, and from two to three months after the start one kidney was removed from each animal for control study and, likewise, to concentrate the effect upon the remaining organ.

Elevation of the blood calcium on this regimen was at times difficult to obtain and still more difficult to sustain, though figures of from 12 to 15 mgm. per cent and, in a few instances, 17 to 19 mgm. were recorded. The kidneys removed in the middle of the experiment were all completely negative, both macroscopically and microscopically. Of the remaining kidneys, on which the dogs lived while the experiment was continued for from two to three months longer, 1 was completely negative, though a bladder stone was present, and 7 showed microscopically scattered deposits of calcium salts. This calcium was found rather uniformly distributed throughout cortex, medulla, and papillæ, and, for the greater part, could be recognized as intratubular deposits, though some

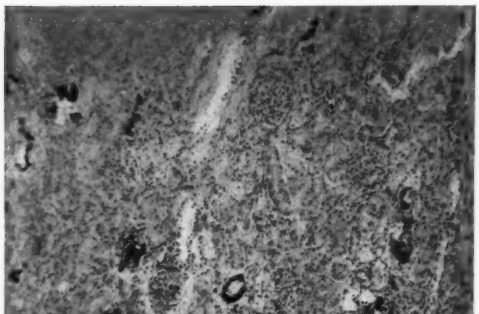

Fig. 25. Cortical calcium salt deposition in case of human hyperparathyroidism.

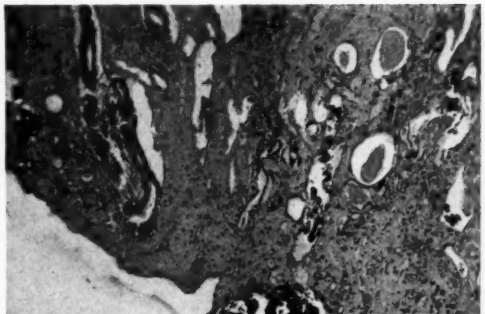

Fig. 26. Papillary calcium-salt deposition in case of human hyperparathyroidism. Note similarity to experimental dogs, and damage to tubular epithelium; also that calcium salts are deposited throughout cortex, medulla, and papilla.

damage to tubule lining cells, with at times calcium deposition in and under same, could be found.

We reported that in 1 dog, in whom a six-month period of administration was accomplished and who had received in this interval 6,240 units of parathyroid extract (parathormone), we observed a typical calcium plaque identical to our Type I Lesion as observed in man in our autopsy series, but there was no evidence of stone growth therein, for it was still subsurface (Fig. 22). Of course, it was quite presumptive to accredit to the administration of the parathyroid extract the entire etiology of this one lesion, as primary renal calculus in the dog is not unusual (we have observed a unique case with stone attached to the papilla), and this plaque might have been but a fortuitous observation.

But our first series left much to be desired, and it was decided to repeat the work with certain details for closer observation. Our second series comprised 16 adult dogs, and treatment was started September 23, 1937, and ended May 4, 1938. Daily injections of the same preparation—parathormone—were given subcutaneously. A small dose, calculated on the animal's weight and varying from 5 to 20 units, was used at starting. This dosage was gradually increased at intervals as tolerance became evident, but again rest periods of a few days were necessary occasionally to offset overadministration. Most dogs were receiving around 600 units daily as they approached the end of their experimental time.

Extensive clinical records and post-mortem studies were made by Dr. Paul R. Leberman of the Urological Staff, University of Pennsylvania, who conducted these experiments in the Department of Research Surgery, all of which are to be reported elsewhere by him. The kidney pathology alone interests us here. Whereas in the first group of dogs we sacrificed one kidney in the mid-experimental period, to find them all macroscopically and microscopically negative, in this second group of dogs we allowed both kidneys to remain until the autopsy, but in each instance took one for microscopic study and the other for special alizarin calcium staining and clearing of the specimen by the modified Schultze method. The latter was done in the hope that we could demonstrate visually the location of calcium deposition in the kidney in an entire specimen.

Gross pathology. At autopsy renal congestion was usually marked, and grayish striations were visible on sectioning. The renal papilla appeared especially hyperemic, and in several (7) specimens papillary deposits suggestive of calcium-salt deposition were macroscopically visible. Two dogs in this series had bladder calculi at autopsy, but

none showed any calculus, gravel, or even sand in the renal pelves or in the ureters.

Microscopic pathology. Eight of our 31 dogs died from some extraneous cause within three weeks of starting the parathormone administration. Nevertheless their kidneys were studied, and each was negative for any evidence of epithelial damage or calcium-salt deposition. Of the 23 remaining dogs, in which administration had been carried on from one to six months, all but 1 showed excessive amounts of calcium salts as intratubular deposits. The 1 exception is unexplained, but interesting, for treatment had extended for four months, but at no time was the blood calcium recorded higher than 12.3 mgm. per cent. The degree of renal calcinosis varied markedly among the dogs, and it appeared to be most pronounced when the animal succumbed or was sacrificed at a time when the hypercalcemia was high, and it is to be supposed that during a regression in the amount of blood calcium the kidneys may rid themselves of some of their tubular deposits.

In this second series again 1 dog (No. 294) showed a suspicious papilla which, on microscopic study, revealed a calcium plaque identical to our human specimens (Fig. 23). The glomeruli showed no noteworthy lesions. The lumina of the convoluted tubules were enlarged and contained granular detritus; the lining cells for the most part were damaged and desquamating. This was true also of the lining epithelial cells of the collecting tubules, which gave the impression that the primary insult had been an epithelial-cell damage from some toxic agent. The lumina of many tubules were filled with inspissated calcium salts, while here and there were seen small calcium-salt deposits in the interstitial tissue. A typical superficial, but subsurface, calcium plaque was near the tip of the papilla and extended completely across the low power field of the microscope. There was no evidence of infection present.

Of the remaining dogs' kidneys 79 per cent showed calcium-salt deposition, and like in the description just given, it occurred rather uniformly deposited, though in differing amounts, throughout the cortex, medulla, and papilla. Some collecting tubules with intact but compressed epithelial lining show their lumina filled with calcium salts. Other tubules, again filled with calcium salts, show no remaining trace of their lining epithelial cells, but show deposition of calcium salts extending into and beyond the basement membrane. In the most advanced specimens calcium deposits can be found even in Bowman's capsule (Fig. 24).

As we have had the privilege of studying 3 human cases at autopsy, in which hyperparathyroidism was part of the clinical diagnosis, with confirmation at necropsy, brief résumés of the renal findings are incorporated here, through the interest and co-operation of Dr. John Eiman. They lend direct substantiation to the animal evidence that damage to the epithelial cells must precede true calcium-salt deposition outside the tubule lumina, and that, lacking such damage, the only deposition occurs as a calcium-salt inspissation within the undamaged tubules.

CASE 1. Female, age 46. Bryn Mawr Hospital (kindness Dr. Strumia). Adenoma of inferior parathyroids. Blood calcium 26 mgm. per cent; phosphorus 3; blood urea nitrogen 51; phosphatase 4.1 units (normal); total plasma protein 10.2 gm.; albumin 5; globulin 5.2. The kidney showed grossly no noteworthy lesions. Microscopically, there were a few small collections of round cells in the cortex, and occasional hyalinized glomeruli. Bowman's capsules were slightly thickened. Nuclei of glomerular tufts were prominent and slightly increased numerically. A few glomeruli showed broken down tufts and escape of red cells into the space of Bowman. The arterioles and smaller arteries showed swelling of endothelial cells, and the larger arteries revealed early arteriosclerotic changes. The proximal parts of the renal papillæ showed moderate increase of interstitial connective tissue and obliteration of some collecting tubules. Most loops of Henle and open collecting tubules showed retrograde changes in the lining epithelial cells, and partial or even complete desquamation. A few of the loops of Henle and the collecting tubules showed their lumina filled with amorphous calcium salts, while the lining epithelial cells of the tubules were compressed but otherwise showed no changes. This obviously is a case of simple inspissation or precipitation of calcium salts in the uriniferous tubules without any pre-existing damage to the lining cells. Lumina of other tubules filled with calcium salts showed almost complete destruction of the lining epithelium and the presence of calcium salts in and beyond the basement membrane. Calcium salt was also seen in the convoluted tubules, in which at best only fragments of the lining epithelium could be demonstrated. Here and there small deposits of calcium salts were seen in the interstitial tissue, which is especially the case near areas of round-cell infiltration. The glomeruli and the capsules of Bowman showed no calcium-salt deposits.

From a study of this specimen it becomes apparent that the calcium deposits occur in (1) the lumina of the loops of Henle and collecting tubules with fairly normal epithelial lining, and (2) in apparently damaged or necrotic epithelial cells of convoluted tubules, their basement membranes, and interstitial tissue.

There is definite evidence in this specimen of renal damage by some unknown toxic material. The changes in the glomeruli and tubules have been described. Further, the presence of round-cell infiltration is definite evidence of the action of an irritant. It would appear that the action of the toxic substance, by damaging the lining epithelial and interstitial tissues, predisposed or facilitated

the deposition of calcium salts. The few loops of Henle and collecting tubules with comparative normal lining of epithelial cells containing calcium salts represent simple inspissation (calcium infarction). *We feel that it is safe to assume that if a toxic agent had not damaged the cellular structures before the occurrence of hypercalcemia, all the calcium in the kidney would be found inspissated in the lumina of the tubules.*

CASE 2. Female, age 37. Abington Hospital. Bone cyst in the acromion process of the scapula; calcium absorption of long bones and skull; marked hyperplasia of all four parathyroids. Kidney: arteriosclerotic nephrosclerosis; chronic glomerulonephritis; tuberculous pyelonephritis and marked calcareous deposits in non-tuberculous areas. Phosphatase 5.2–6.5; blood urea nitrogen 286–45; chlorides 422–648; carbon dioxide 14–53; phosphorus 3.7—10.1; total base 127–155; calcium 10.4–9.3.

Microscopic study of the kidney showed all of the glomeruli near the tuberculous areas either partially or completely replaced by connective tissue, and showing deposits of calcium which assumed the shape of the glomerulus or a ring with cellular detritus in the central part. The further away from the active tuberculous foci, the more normal the glomeruli were, so that some of them showed no noteworthy lesions. However, there were exceedingly few normal or near normal glomeruli, which accounts for the marked renal dysfunction. No calcium deposits were seen in the convoluted tubules; and the tips of the papillæ had been destroyed by the tuberculous process.

From the study of this specimen it is very striking that the nearer the glomerulus is to an active tuberculous focus, the more marked are the calcium-salt deposits, or conversely, the further the glomerulus is from an active tuberculous focus, the nearer normal it is in appearance. It is safe to state that the action of toxic material (in this case toxins liberated by the tubercle bacillus) predisposes to the deposition of calcium in the glomeruli and their capsules.

CASE 3. Male, age 20. Abington Hospital. Hyperplasia of all four parathyroids—combined weight 2.45 gm.; chronic glomerulonephritis; decalcification of small long bones, hands, and feet. Blood urea nitrogen 250–190; plasma carbon dioxide 21–59; calcium 6.8; phosphorus 18–13.2. Kidneys grossly 45 and 60 gm.; typical chronic glomerulonephritis.

Microscopic study of the kidney revealed advanced chronic glomerulonephritis. Here and there were seen a few round cells. Many glomeruli had been converted into connective-tissue masses. A few glomeruli showed partial hyalinization, and a very occasional one approached the normal. The partially damaged glomeruli showed the greatest calcium-salt deposits. Some calcium-salt deposits were seen in what seemed to be remnants of collecting tubules, and small amounts occurred in the interstitial connective tissue. The papillæ showed marked fibrosis, obliteration, and cystic dilatation of many collecting tubules, and calcium-salt deposits everywhere (Figs. 25 and 26).

Discussion. From these experimental studies on dogs, and from the pathology observed in the 3 human cases of hyperparathyroidism, it becomes quite evident that some damage to the epithelial cells lining the renal tubules precedes true calcium-salt deposition in this condition. That this damage may even extend to the intertubular connective-tissue structures seems likewise proved. Of especial interest is that in 2 of these experimental dogs we have been able to reproduce the calcium-plaque formation of the human kidney, and only in this parathormone study have we observed both Type I and Type II papillary pathology, which our autopsy material has already related to the development of primary renal calculi. Hanes (1939) in a recent article states that "tissue necrosis unquestionably precedes the deposit of calcium in hyper-parathyroidism," and quotes both McJunkin, Tweedy, and Breuhaus, working with rats, and Cantarow, Stewart, and Housel, using dogs, in making similar conclusions.

I believe it to be true that some of our experimental dogs had only tubular inspissation of calcium salts, and that such is to be interpreted only as evidence of the hyperexcretory state, and in such cases this material may wash out if the hypercalcemia decreases. However, when actual tissue damage occurs, and calcium salts are deposited therein as part of nature's effort to repair such injury, then the permanency of this pathological picture does not change.

CONCLUSIONS

H. G. Wells many years ago stated that "in mammals only one normal tissue is the site of calcium infiltration—the developing bone; while *any* tissue may become calcified, provided its vitality is reduced sufficiently and that it remains long unabsorbed," and again, "In calcification we have deposited in dead tissues, or any tissue of low vitality, a considerable quantity of inorganic calcium salts, which appear at first in granular form, although later there may be more or less fusion and resulting areas of homogeneity."

From the material herein presented it becomes evident:

That in the absence of stasis, a primary renal calculus is dependent upon, and arises because of, a pathological condition of the renal papilla.

That the pathological condition is a varying degree of damage to the structures of the collecting tubules and the supporting interstitial tissue.

That this damage is succeeded in the living by attempted repair, in which process calcium salts may be deposited.

That such calcium-salt deposition may be both intratubular and extratubular, and of varying

degree; in some cases, slow, discreet, and chronic; in others, acute, rapid, and overwhelming.

That from our autopsy studies two types are distinctly discernible; to wit: Type I, a calcium plaque with a predominance of interstitial deposition, and evidencing a slow, chronic process; Type II, an intratubular deposition giving the picture of a more drastic process and a more rapid accumulation.

That in Type I calcium carbonate and calcium phosphate have been identified, and it is suggested that calcium nucleinate may make up the remainder.

That in Type I calcium-salt deposition is most frequently on the side wall of the papilla, and remains innocent of any part in the causation of stone until growth and pressure (decubitus) brings it to the surface of the papilla.

That when such a calcium plaque does become exposed on the surface of the papilla, it is then bathed in calycine urine and, acting as a foreign body, becomes the nidus upon which *any* urinary salt may crystallize.

That calcium-phosphate, calcium-oxalate, and uric acid calculi have been identified in such origin and growth, and it is to be expected that other salts will be so identified in the future when technical difficulties are overcome.

That on this pathological basis it can be recognized how a stone gains an opportunity to grow and also to remain asymptomatic over long periods of time.

That when a calculus is extruded, there is evidence presented that such is accomplished by the tearing of its foundation of calcium-salt deposit from the papilla.

That in Type II the calcium salts are principally intratubular and may present all gradations from simple tubular inspissation to drastic choking of the tubules and marked tubular damage, with some interstitial deposition in advanced cases.

That in Type II only calcium phosphate has been identified in the tubular process and only calcium-phosphate calculi observed to form thereon.

That in the Type II lesion the picture is that recognized as calcium infarction of the papilla, and any stone formation occurs at the papillary tip where the morbid process is most advanced.

There are presented the results of 1,154 postmortem studies, wherein Type I lesion has been observed in 19 per cent, and Type II lesion in 1.9 per cent, and wherein 65 examples of calculus growing adherent to the renal papilla have been observed.

There is new evidence presented from studies on rabbits that the kidney secretes toxins, that the kidney concentrates toxins, and that, as a result, damage to the epithelial cells lining the collecting tubules of the papilla occurs. In this study repair by calcium-salt deposition has not as yet been observed, and difficulty has been experienced in minimizing the toxic insult for prolonged effect and study.

There is evidence presented from studies on 112 rats on Vitamin-A-deficiency diets that the renal tubule epithelium suffers primary damage, and, in advanced stages, secondary calcium-salt deposition occurs.

There is evidence presented from 3 human cases of hyperparathyroidism and 32 experimental dogs to which parathyroid hormone was administered to show that in this condition the initial renal damage is to tubule epithelium, and that it precedes the characteristic calcium-salt deposition.

It is to be pointed out that in none of these studies, entailing a vast amount of histological material, has local renal infection manifested itself, with the exception of 8 cases from the autopsy series exemplifying the Type II lesion and 9 cases of the Type I lesion.

Therefore, the following conclusions are offered:

That in the course of its normal function the kidney suffers insults from many directions, and the greatest damage therefrom occurs in the convoluted and, especially, the collecting tubules of the renal papilla, where the greatest concentration of both normal and abnormal urinary elements occurs. That from these research studies we have been able to prove that primary renal calcification is a repair response to certain morbid states in the renal papilla, that damage to the epithelial cells lining the renal tubules occurs early, and that this damage is the prime essential to the subsequent permanent deposition of calcium salts. That one must bear in mind constantly that the degree of damage and the degree of calcinosis are extremely variable, both in amount and in location, and may be from quite variable origins. That if such calcium-salt deposition is extensive and progressive at some point, it reaches the surface of the papilla, and it then becomes bathed in calycine urine and acts as the nidus upon which urinary salts begin to crystallize.

It may be suggested that the salt deposited as a calculus will be the one most ready to crystallize out of solution, be that due to abundance, to disturbed colloidal balance, or to the poorly understood laws of crystallization. Here we have for the first time a common origin for the diversification of chemical constituents of the composi-

tion of stone. Here we have an explanation of *where* a stone forms, *why* a stone forms, and *how* a stone forms, and also an accounting for the static and asymptomatic state during which a stone slowly gains growth.

And, finally, now as we have learned to consider stone as only a symptom of some preceding pathology, again it appears that any type of calcium-salt deposition in the renal papilla is only incidental to an antecedent (tissue) damage which, in its turn, may arise from various sources, and that several concurrent factors are always required in the formation of a renal calculus.

Treatment. From published reports hyperparathyroidism may be expected to account for not more than 5 per cent of the clinical cases of primary renal calculus. That hypovitaminosis A can be responsible is to be recognized, but in modern civilization it probably can account for but a small portion of the remaining 95 per cent, and we would be generous to credit it with as much as 10 per cent of the cases of primary renal calculus. It is the belief of the author that the products (toxins) of distant focal infection play a very major rôle in the causation of papillary pathology and the etiology of stone. The close relationship that exists between the so-called calculus age and that of focal infections—twenty-five to fifty years—has never been pointed out, and while clinical studies are too uncertain to be trusted, it has been our constant observation that patients with primary renal calculi consistently have active focal infectious conditions elsewhere. One must not lose sight of the undoubted fact that toxins other than bacterial (disease, metabolic, dehydration) may produce a similar renal response.

So the treatment and prevention of primary renal calculus embraces a broad study of the individual patient, an intelligent analysis and control of his urine, and the correction of pertinent factors, most of which are quite distant from the seat of disease.

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ABSTRACTS OF CURRENT LITERATURE

SURGERY OF THE HEAD AND NECK

HEAD

Kettel, K.: Osteomyelitis of the Frontal Bone. Surgical Treatment: Which Way of Approach is the Best? *Arch. Otolaryngol.*, 1940, 31: 622.

Osteomyelitis of the frontal bone may be extraordinarily dangerous, because of the rapidity with which it spreads and the frequency with which it is followed by intracranial complications. The operation for this condition has two purposes: first, to remove all the diseased part of the bone and to drain possible deep-seated inflammation (leptomeningitis, epidural abscess, or possibly abscess of the brain); and, second, to clean out and drain the sinuses from which the infection has originated.

The bone affected by osteomyelitis behaves as though it contained a malignant tumor. The resection must, therefore, be performed in healthy tissue. It may be difficult, and it is sometimes impossible, even during the operation, to decide with certainty where the bone is healthy. Before the operation it is impossible to do so.

Kettel finds that unrestricted access for resection of the frontal bone and the adjacent parts of the parietal bone, the frontal sinuses, the ethmoid labyrinth, the roof of the orbit, and the lamina cribrosa is obtained by a coronal incision above the hair line, which permits reflection of the scalp covering the forehead forward over the face. The cicatrix is concealed by the hair, and, as no branches of the facial nerve and no muscles have been cut, and as no tense scars are to be found on the forehead, the cosmetic and mimetic results are ideal.

NOAH D. FABRICANT, M.D.

Szeker, J.: Facial Bone Fractures (Brueche der Gesichtsknochen). *Arb. chir. Klin. Univ. Pécs*, 1939, p. 219.

The facial bones consist of the nasal bones, the vomer, the inferior turbinated bones, the lacrimal bone, the superior maxilla, the zygomatic bone, the palatum durum, and the inferior maxilla. Since injury to the lacrimal bone belongs in the sphere of the ophthalmologist, and injury to the maxilla in that of the dental surgeon, the author disregards these two.

Fractures of the nasal bones, representing independent bone fractures, occur after comparatively unimportant traumas (blows, boxing); a more violent traumatic influence is associated with injury to other facial bones as well. There are lateral and bilateral injuries, and they are usually internal, situated toward the nasal passages. Diagnosis is easy. A roentgenogram, preferably taken from two angles, will throw light on difficult cases. Treatment is simple and consists of the reposition of the bone which may be displaced, or of the entire nose which may be displaced to one side; reposition is followed by adequate fixation with a Josef or Fruehwald nose clamp, or with a cast. The nasal passages must receive special attention; postoperative strictures accompanied by respiratory and olfactory disturbances are not easily corrected.

An isolated fracture of the vomer is rare. This, as well as a fracture of the inferior turbinated bones, is usually a manifestation accompanying fracture of the superior maxilla. Also the isolated fracture of the superior maxilla is an infrequent occurrence; it follows more violent injury and, as a rule, is complicated with fracture of the zygomatic bone. The three Le Fort fracture lines are considered the ones most frequently encountered, but in addition to these typical ones, there are fracture lines in other directions. The main symptoms are hemorrhage in the soft tissues and facial cavities; the hemorrhage may become so severe that ligature of the carotis externa may have to be considered. In cases of nerve injury it is principally the second trigeminal ramus which is involved, followed by a slight paresthesia or a complete anesthesia; a subsequent manifestation is neuralgia. Lockjaw, injury to the eye, and other disorders, including disturbances in salivation, paralysis of the palatum molle, and lesion of the inner cranium occur.

Regarding injuries to the superior maxilla, two groups may be distinguished: (1) bone fissures and minor bone displacements, which in regard to future function are of no importance; they require no special interference, and (2) major fractures.

Among the 20,000 recumbent patients in the Clinic, 3,000 suffered from bone fractures; among these were 116 skull injuries, of which 12 were fractures of the superior maxilla. Three of these cases required surgical interference. This implies the Luc-Caldwell method, consisting of opening of the proper superior maxillary cavity, removal of the hemorrhagic extravasate, reposition of the displaced bones with tamponade, and suture. Special attention should be given an eventual injury to the nerves, or their exposure to pressure from the fractured bone ends and bone splinters.

In the treatment of fractured superior maxillary bones there are two possibilities which must be borne in mind: infection and plastic exudate. A fractured superior maxilla, generally caused by a violent injury, is often associated with a fracture of the zygomatic bone, and the fractured end is usually forced into the superior maxillary cavity. In such cases it is necessary to expose the sinus maxillaris.

Various methods are cited for the reposition of a fractured zygomatic bone (Matas, Garner, Gilies, Hoefer, Luc-Caldwell). Particular care should be given the treatment of the teeth.

Summing up, the author explains that in judging injuries to the facial bones the following rules should be considered: (1) treatment of the injured soft tissues alone is insufficient; for proper healing the examination of the nose and its neighboring cavities is absolutely necessary; (2) in injuries of the secondary cavities, infection and plastic exudate require special consideration; and (3) since the advantages of exposing the sinus maxillaris are recognized, this method should be used in suitable cases.

(E. Illés). Hilda H. Wullen.

EYE

Davis, F. A.: Primary Tumors of the Optic Nerve (A Phenomenon of Recklinghausen's Disease): Clinical and Pathological Study with a Report of 5 Cases and a Review of the Literature. *Arch. Ophth.*, 1940, 23: 735, 957.

In this very detailed, comprehensive, and well illustrated treatise, the author brings out some points that seem to require further research for confirmation or disproval. He states: "This paper is a clinical and pathologic report of tumors of the optic nerve associated with Recklinghausen's disease, based on a study of 5 cases and a review of the literature."

So-called primary tumors of the optic nerve usually appear as one of two types, namely, gliomas and endotheliomas, the former being much the more common. Endotheliomas resemble those found in the brain, known as meningiomas or meningeal fibroblastomas. They arise from the dura or arachnoid sheath of the nerve or at times by extension from similar growths within the cranial cavity.

This study indicates that glial tumors start with an abnormal proliferation of the normal adult types of neuroglia of the nerve stem. After varying periods of growth, the abnormal neoplastic neuroglial cells penetrate the pia, with the formation of a gliomatous tumor in the sheath. Proliferation of the mesothelial cells of the arachnoid follows the glial penetration of the pia, with the formation of a tumor-like mass in this portion of the nerve sheath. Later, intermingling of the proliferated cells from these two areas produces a complex histological structure, the precise nature of which is difficult to interpret unless earlier stages of the growth have been studied.

Study of sections from these tumors reveals five different stages in the evolution of their growth.

Since these growths exhibit all the characteristics of true tumors, they should be designated as gliomas. Such terms as gliomatosis and astrocytosis should be used merely as descriptive terms for the earliest phase of their development. Complete histogenesis of the neoplastic cells has not been determined. Such types as spongioblastoma, spongioneuroblastoma, astrocytoma, and oligodendrocytoma have been reported.

The outstanding feature of the neoplastic cells was excessive fiber formation within as well as without the nerve stem. This, together with the general character of the cells as revealed by special staining, indicates that predominant cell types were astrocytes, so that these tumors are designated astrocytomas.

The 5 cases herein reported were all associated with the abortive type of Recklinghausen's disease. Other lesions, such as plexiform neurofibromatosis of the orbit and globe, were present in 1 case, while manifestations of involvement of the central nervous system, such as gliosis of the chiasm and other areas of the brain, and a glioma of the temporal lobe of the brain were also encountered.

The review of the literature reveals at least 32 authentic cases of tumors of the optic nerve associated with Recklinghausen's disease. Many other cases of the latter disease, in which reduced vision and atrophy of the optic nerve were reported, probably fall within this classification. This association can no longer be considered as merely coincident.

The cause of Recklinghausen's disease and related lesions is not known. Pathologists are in disagreement concerning the nature of the tumors which accompany the disease. The lesions which make up this syndrome are more widespread than at first believed. One group of pathologists maintain that tumors of the peripheral nerves arise from some defect in the sheath of Schwann cells, a neuro-ectodermal derivative, while others assert that they arise from the fibrous elements of the nerves.

Studies of Del Rio Hortega, which are endorsed by Penfield, indicate that the oligodendroglia of the central nervous system, which includes the optic nerve, is homologous with the Schwann cells of the peripheral nervous system. A similar function of these two cell elements, namely, maintenance of the myelin sheath of the nerve, is therefore probable. A defect of these homologous structures has been suggested by Del Rio Hortega as a common source of origin of tumors of the optic nerve and tumors of the peripheral nerves.

Attempts to find some common background for all the tumors which make up the Recklinghausen syndrome, as now known, are complicated by the great dissimilarity in structure of some of the tumors. This suggests that the primary lesion in this complex disease must be sought in some degenerative change which primarily affects the nerve substance itself, while the tumors which follow may be secondary growths in the various supportive elements.

That tumors of the optic nerve probably belong to a system disease, as originally suggested by Emanuel, is borne out by the simultaneous appearance of multiple lesions in the central and peripheral nervous systems, by the fact that the tumors are bilateral at times, and, further, by the fact that multiple involvement of the nerve has been reported. The slow rate of growth and the relatively benign nature of the tumors are characteristic of other lesions associated with this syndrome.

This study and review of the literature have led the author to conclude that tumors of the optic nerve are in many, if not most, instances but a part of a more widely disseminated lesion of the peripheral and central nervous systems, commonly referred to as neurofibromatosis, or Recklinghausen's disease.

The term "neurofibromatosis" or "neurofibroma" as applied to tumors of the optic nerve should be abandoned, for they are usually gliomas or endotheliomas.

LESLIE L. MCCOY, M.D.

EAR

New, G. B., and Erich, J. B.: Protruding Ears: A Method of Plastic Correction. *Am. J. Surg.*, 1940, 48: 385.

Among the most engaging of purely plastic surgical problems is the correction of protruding deformities of the ears. By a process of trial and error the surgical technique has undergone a series of gradual steps toward perfection. There is yet opportunity for improvement. Few of us realize the amount of mental discomfort endured by some sensitive individuals who have abnormalities such as this. When this deformity is the fundamental basis for an obsession or an inferiority complex, correction of the abnormality promptly removes the mental or emotional symptoms. Then, too, it is a matter of common knowledge that even a few intelligent and well-educated people find it impossible to obtain certain types of positions because of this deformity.

An outstanding ear is the result of a congenital malformation of the anthelix. The embryological factors which produce this flattening or concavity of the anthelix are unknown. To make a broad statement, it might be said that the cephalo-auricular angle is decreased in proportion to the increase of convexity of the anthelix. This generalization, as a matter of fact, forms the basis of treatment in the more recently devised operations for the correction of outstanding ears; the aim of these surgical procedures is to restore to the anthelix its normal convexity, which, in turn, mechanically deflects the ear inward toward the head.

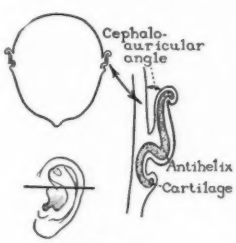

Fig. 1

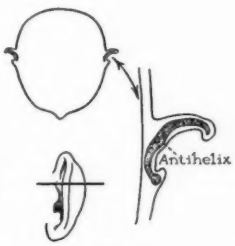

Fig. 2

Fig. 1. Cross section of a normal ear illustrating the marked convexity of the anthelix.

Fig. 2. Cross section of an outstanding ear illustrating the flattened anthelix and the resultant protrusion of the scaphoid and helical portions of the auricle.

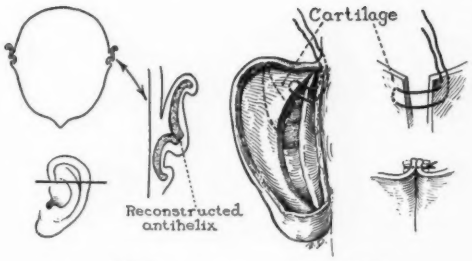

Fig. 3 Fig. 4

Fig. 3. Cross section of a reconstructed protruding ear. After excising an elliptical strip of cartilage, correctly inserted mattress sutures evert the cut edges of the cartilage so as to produce a normally convex anthelix, which, in turn, rectifies the abnormal state of protrusion.

Fig. 4. Diagram of the posterior surface of a protruding ear. The skin has been entirely removed to give a better view of the auricular cartilages. This drawing illustrates the elliptical strip of cartilage which has been removed, and the method of inserting mattress sutures from the anterior surface of the ear through skin and cartilage. On tying these sutures over small cotton rolls, the cut edges of the cartilage are everted to produce a convex anthelix. The dotted margins of the triangular area on the upper portion of the auricular cartilage indicate the site at which a secondary wedge of cartilage may be removed for the construction of a convex posterior crus; this procedure counteracts any tendency of the upper portion of the ear to lop forward.

(Courtesy of Am. J. Surg.)

The deformity can be corrected satisfactorily at almost any age. A child with outstanding ears is best operated on when he is about five years old, before entering school, so as to preclude the possibility of his developing emotional disturbances as a result of the abnormality. Such operations at this early age apparently do not interfere with the subsequent normal growth of the ears. In the majority of cases of protruding ears, the technique as described will correct the deformity very satisfactorily.

Gniloryboff, T. E.: Plastic Reconstruction of the External Ear. *Nov. khir. arkh.*, 1939, 45: 148.

Reconstruction of the external ear is most frequently indicated after traumas, burns, frost bites, and congenital malformations; less frequently the operation is performed after the excision of tumors. Corrections of partial defects of the external ear can be accomplished according to the numerous methods, but the greatest difficulties are encountered in cases in which a complete reconstruction of the ear is necessary. Gelatin prostheses, formation of pedunculated flaps from the skin of the neck, and transplantation of cartilage have been suggested, but the plastic methods have not yet been perfected.

The author reconstructed 7 ears in 6 patients, by transplantations of rib cartilage. All of the patients were men, and the operations were performed under local anesthesia. In 4 instances the external ear was absent entirely and in 2 partially. The tubular flap was prepared from the chest or dorsal region. A

few months after the flap healed in, a fragment of a rib cartilage was implanted through an upper-posterior incision. The author advises exposure of a costal arch close to the sternum. He removes the cartilage of two adjoining ribs in order to prepare the fragment with a satisfactory oval outline. Several minor operations may be required to improve the cosmetic results. JOSEPH K. NARAT, M.D.

NOSE AND SINUSES

Van Dishoeck, H. A. E.: Nasal Plethysmometry As a New Test for Sinus Thrombosis. *Arch. Otolaryngol.*, 1940, 31: 588.

A new test for sinus thrombosis is described by the author. The technique is based on the fact that compression of the healthy jugular vein while the other jugular vein is obstructed, in most cases, causes congestion of the wide venous spaces of the nasal turbinates. The swelling of the conchæ can be seen in some cases by anterior rhinoscopic examination, but it can be clearly demonstrated in every case by means of a simple apparatus, the nasal plethysmometer.

This apparatus consists of two small inflatable rubber balloons, each of which is mounted on one leg of a small manometer. When one of these balloons or both are introduced into the nose, one can blow them up without displacing the meniscuses by means of the bridge, while the clip is placed on the rubber connection. When the bridge is closed with the clip on the rubber connection, every variation in conchal swelling will result in a displacement of the manometer fluid.

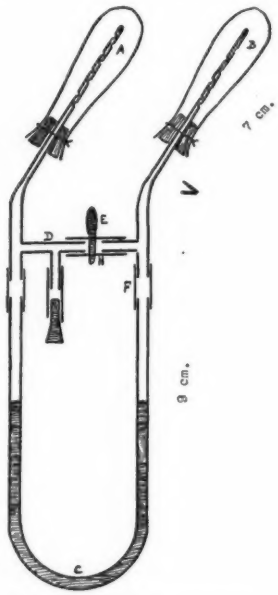

Fig. 1. Nasal plethysmometer.

The instrument can be used in two ways: in one the balloon is introduced into the nose on the side where the jugular vein will be compressed first and then on the other side; in the other one balloon is introduced into each nostril. In a normal patient slight pressure on the left jugular vein will cause slight swelling of the left concha and no swelling, or very little, of the right one. Pressure on both jugular veins causes considerable swelling in both nasal passages. On anterior rhinoscopic inspection, especially, the detumescence when the pressure on the veins is released is clearly seen.

In a case of sinus thrombosis on the left, pressure on the left side of the neck does not produce swelling, while pressure on the right side causes considerable swelling of the right turbinal and a little swelling of the left turbinal. The positive symptom is thus the marked difference in the conchal swelling when pressure is applied on the healthy side from that when it is applied on the obstructed jugular vein. A preliminary nasal examination is necessary because the experimental result may be invalidated by the following circumstances: (1) the presence of too little cavernous tissue, on account of nasal crests, operations, or atrophy; (2) previous swelling of the nose to its utmost capacity; and (3) obstruction of the venous connections of the nose and the endocranial system; i.e. in thrombosis of the cavernous plexus. A definite positive result is diagnostically valuable. Only with congenital aplasia of the sinus is confusion with thrombosis possible.

NOAH D. FABRICANT, M.D.

Pfahler, G. E., and Vastine, J. H., 2d: The Roentgen Diagnosis of Cancer of the Accessory Sinuses. *Arch. Otolaryngol.*, 1940, 31: 561.

To think of the possibility of cancer of the accessory sinuses is the first essential in making the diagnosis. One or many of the following signs and symptoms should suggest cancer of the nasal and paranasal cavities: (1) a sense of fulness in the nose—partial or complete nasal obstruction, usually unilateral; (2) nasal discharge—either mucopurulent or serosanguineous; (3) pain—headache if the superior anatomical section is involved, and neuralgia if the alveolus or the floor of the antrum is involved or if the fifth nerve or its branches are involved; (4) fetid odors, if necrosis or ulceration is present; (5) change of the nasal tones of the voice, due to nasal obstruction or blocking of the antrum; (6) loss or alteration of the sense of small; (7) in late stages, expansion or destruction of bone, due to pressure atrophy or invasion by the tumor, with swelling of the face, swelling of the alveolus, and loss of the teeth; (8) invasion of the orbit producing such signs as exophthalmos and proptosis; (9) ulceration of the tumor in naris, giving rise to hemorrhage; (10) invasion of the skin with edema and later ulceration; (11) local extension to the base of the skull, with consequent neurological

symptoms; (12) metastasis to the regional lymph nodes, causing dysphagia and dyspnea; and (13) distant metastases, producing symptoms which vary with the site. Most of these signs and symptoms are encountered late in the disease.

Unfortunately most diagnoses are made late, and therefore in most cases the condition is incurable. At this time the clinical diagnosis is often obvious, and the roentgenological diagnosis may be characteristic, based on increased density of the sinuses or nares; expansion or destruction of bone; and an irregular outline of the soft tissues shown by opaque mediums. Consequently, in such a serious disease every possible means of diagnosis must be utilized. This includes the careful taking of the history, thorough clinical observations, and a thorough roentgen investigation, with an adequate number of projections and detailed study. Finally, a biopsy is essential for the early diagnosis.

Cancers involving the accessory sinuses vary in their distribution and characteristics, according to the types which the authors describe at length. The treatment and management will vary with these types. In some cases, irradiation alone will give the best results. In other cases, a combination of surgical or electrosurgical measures and irradiation will give best results. Individual consideration is absolutely necessary in each case, in which the type of disease and its location, extent, and duration, especially, must be taken into consideration.

NOAH D. FABRICANT, M.D.

MOUTH

Keaster, J.: Studies on the Anatomy and Physiology of the Tongue. *Laryngoscope*, 1940, 50: 222.

Keaster states that the tongue, throughout the animal kingdom, is different from other organs of special sense, such as the eye or the ear, in that it serves not one function but several. The tongue in the lower vertebrates has as its most specialized function that of prehension. The tongue of the frog can be thrown in and out with a hinge-like action as the frog goes after food. A snake's tongue can be protruded from the mouth with great rapidity in the act of prehension.

In the lowest animal of the mammalian order, the whale, the tongue is almost a useless organ. It has no prehensile power of function in mastication because of the manner in which the animal eats. Further along in the mammalian order the tongue again assumes its principal function—that of prehension. The anteater's tongue is long, sharp, and easily protrusible; the tongue of the giraffe is long and has very facile movement. It can be twined around small bits of food, such as leaves and twigs.

The function of the tongue as an organ of deglutition and mastication has developed with the change in the manner in which various animal groups eat and the variety of diet which they eat. These functions are found to be most highly developed in the primates.

The sense of taste has developed from nerve eminences all over the bodies of bony fish to highly developed taste buds on the tongue and oral cavities of all mammals but the whale. In man, the sense of taste is most highly developed because of the enormous number of papillæ rising above the level of the epithelium on the dorsum of the tongue, in the buccal cavity, in the fundus of the pharynx, and on the inside of the lower lip.

The musculature of the tongue varies very little from one order to another, with the exception of the musculature of the whale tongue, which, again, through disuse, is almost non-existent. The tongues of the rodents have minute muscles that are the same in structure as those in the tongues of the larger animals. One investigator goes so far as to say that if one were given two tongues, one of a man, the other of an orang-outang, one would have difficulty in differentiating them as they are so similar in structure, size, shape, and papillary arrangement.

The foregoing discussion on the phylogenetic development of the tongue indicates that its prime functions are prehension, mastication, and deglutition. Articulation becomes an added function in man. From the fact that speech is the least impaired of all of the functions in cases of tongue amputation, it was concluded that teachers of speech may have been too empirical about the exact functioning of the muscles of the tongue in speech and when they insist that the tongue is a necessity in the production of aurally acceptable speech. The patients studied have difficulty in deglutition and in mastication, but they can and do speak without a tongue.

Upon dissection of 3 nine-months' fetal tongues, it was observed that the fetal tongue does not differ from the adult tongue in musculature. Its one point of difference is the epithelium on the dorsum: in the fetal tongue the dorsum is smooth to the touch, with undeveloped papillary structures.

This investigation will be continued in order to determine what musculature replaces that of the tongue in the production of the articulate speech of those without tongues. NOAH D. FABRICANT, M.D.

NECK

Lauener, P.: Statistical Investigations of the Incidence of Struma in School Children of the Canton of Bern Before and After the Introduction of Iodized Salt (Statistische Erhebungen ueber den Kropf bei den Schulkindern in Kanton Bern vor und nach Einfuehrung des jodierten Kochsalzes). *Schweiz. med. Wchnschr.*, 1939, 1: 455.

An examination of 30,000 school children which was carried out in 1933 revealed the rate at which struma occurred in the several districts of the Canton of Bern. The formerly known fact that the goiter epidemic is by no means uniformly distributed was hereby confirmed. In addition to the districts with a goiter incidence ranging from 35 to 40 per cent in certain alpine valleys and those in the Jura with an incidence of from 0 to 5 per cent, districts with all intermediary stages are represented.

In 1936 iodized salt was sold in place of ordinary salt by order of the government; uniodized salt was sold only upon special request. In 1938 examination of the school children was repeated, and since the statistics again referred to 30,000 individual examinations, they appear decisive for the entire population. They show unquestionably a considerable reduction in the occurrence of struma since the introduction of iodized salt.

However, struma cannot be entirely eradicated by the use of iodized salt, since iodine deficiency represents only about 75 per cent of the causative factors of goiter. Other causes, particularly social influences, play a certain rôle. Unfortunately, also, the order of the authorities is not strictly carried out, as several merchants arbitrarily continue to sell uniodized salt.

In addition, ever since the distribution of iodine tablets in the schools of the city of Bern was discontinued in the expectation that an iodized salt prophylaxis would suffice, new cases of enlarged thyroids have been observed. On the whole, however, the number of goiter cases has diminished. Boys usually showed better results than girls as the iodine requirement is greater in the female.

(A. BRUNNER). HILDA H. WULLEN.

Cohn, L. C. and Stewart, G. A.: Tumors of the Lateral Thyroid Component. *Arch. Surg.*, 1940, 40: 585.

Up to this report 156 cases of tumor of the lateral thyroid component have been recorded in the literature. The authors add 17 new cases from the Surgical Pathological Laboratory of the Johns Hopkins Hospital. Previously 3 cases had been reported from this laboratory; these 3 cases are also reviewed here. In the majority of cases the clinical diagnosis was incorrect.

Aberrant thyroid tissue deposited during migration of the median primordium has been reported as occurring in various locations in the midline of the neck, from the foramen cecum of the tongue to the definitive thyroid gland. Also, thyroid tissue has been reported as occurring in the nasopharynx, larynx, trachea, esophagus, mediastinum, pleura, pericardium, ovary, and long bones. The present study is limited to consideration of tumors of thyroid tissue located in the lateral regions of the neck, with and without tumors in the thyroid gland resembling them histologically.

The tumors have been divided into three groups: (1) adenocarcinoma of the thyroid gland with metastases to the cervical lymph nodes (7 cases), (2) aberrant malignant thyroid tumor in the presence of a normal thyroid gland (9 cases), and (3) benign aberrant thyroid tumors (4 cases).

In Group 1 there were 6 cases of palpable tumor of the thyroid gland at the time of examination and in 5 instances the tumor was a typical adenocarcinoma. The other tumor was classified as a variant of the papillary adenocarcinoma with marked vascular invasion. The absence of remote metastases many years after involvement of the regional lymph nodes in 5 cases confirms the low grade of malignancy of the majority of these tumors. However, local recurrences were the rule. Distant metastases occurred in 1 case. Two of the patients had slight toxic symptoms. A seventh patient had a tumor of the thyroid gland with local metastases eighteen years after thyroidectomy.

Group 2 consisted of 9 cases of aberrant malignant thyroid tissue in the presence of a normal thyroid gland. There was 1 case with no metastases to the cervical lymph nodes, 5 cases with metastases to the cervical lymph nodes, and 3 cases in which there were metastases to the cervical lymph nodes with no known thyroid or aberrant tumor in the history or on examination, it having been removed previously and not diagnosed, or so involved in the mass of carcinomatous lymph nodes as to be undemonstrable.

In discussing the papillary tumors as a unit, Groups 1 and 2, it was found that the average age of the patient when the tumor was first noted was thirty-five years. There were 11 females and 5 males. There were slight toxic symptoms in only 2 instances. In 7 cases the primary tumor was in the thyroid gland and in 9 cases the primary tumor was in the lateral aberrant thyroid tissue. In 5 cases the location of the primary aberrant thyroid carcinoma was definitely known, in 3 cases it was in the submaxillary region, in 1 case it was in the region of the hyoid bone, and in another case in the supraclavicular area.

The frequency of recurrence demonstrated the necessity of adequate and extensive resection. In spite of the high incidence of recurrence, death from remote metastases occurred in only 2 patients (16 per cent), and in both there was vascular invasion.

In Group 3 (benign aberrant thyroid tumors) there was 1 patient with a palpable tumor of the thyroid, 1 with a tumor of the thyroid previously removed, and 2 with no palpable tumor of the thyroid, nor had such a tumor been removed. Aberrant thyroid tissue can undergo hypertrophy or even compensatory hyperplasia because of a hypofunctioning thyroid gland or because of neoplasia. Histologically it is difficult to differentiate between hyperplasia and neoplasia.

Because of local or regional recurrence after operation in 71 per cent of the papillary tumors in this series the authors urge complete excision and block dissection of the cervical lymph nodes in cases of papillary tumors. EARL O. LATIMER, M.D.

Ward, R.: The Relation of Tumors of Lateral Aberrant Thyroid Tissue to Malignant Disease of the Thyroid Gland. *Arch. Surg.*, 1940, 40: 606.

The author presents 15 cases of tumors of aberrant thyroid tissue, 12 of which he considers malignant and 3 benign. Each case is discussed, giving his reasons for classifying the growth as benign or malignant. He states that only the passage of time and eventual outcome will prove whether the tumors are malignant. Since tumors of aberrant thyroid tissue are of such a low grade of malignancy and many malignant tumors of thyroid tissue in general

have a tendency to lie dormant or to progress very slowly over many years, a long period of observation in addition to a rigid follow-up in all cases is necessary before conclusions can be drawn.

In 4,274 operations from which material was available for study there were 15 tumors of lateral aberrant thyroid tissue and 95 malignant growths arising in normally situated thyroid glands. The average age of the patients with malignant tumors of a lateral aberrant thyroid was twenty-four years, while the average age of the 95 patients with malignant tumors in the normally placed thyroid was fifty-two and seven-tenths years. Fifty-eight per cent of the patients with malignant tumors arising in lateral aberrant thyroids were under thirty years of age while only 7 per cent of the malignant tumors of the midline appeared in the first three decades of life.

The mortality for the malignant tumors of lateral aberrant thyroid origin as compared to that for the tumors arising in the midline gives a ratio of 25 to 53.3.

The ratio of males to females is 1:1.4 for malignancy of the lateral aberrant thyroid as compared to 1:3 for the midline malignant tumors. The most common location of the tumors is along the course of the sternocleidomastoid muscle. Other locations were in the inferior carotid and subclavian triangles.

EARL O. LATIMER, M.D.

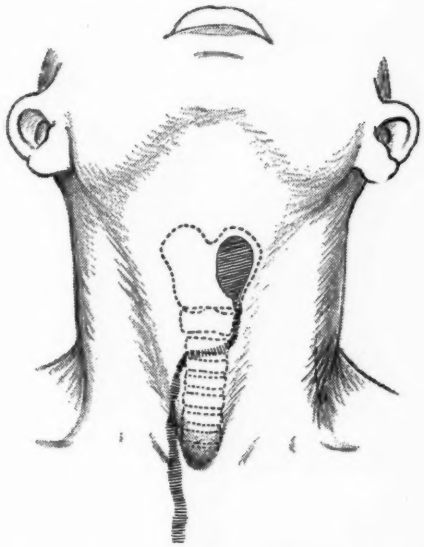

Fig. 1. An abscess in the larynx behind the left thyroid plate and in the piriform fossa has broken through the cricothyroid membrane and burrowed downward behind the trachea into the right side of the mediastinum.

Schugt, H. P.: The Piriform Sinus: Anatomical and Clinical Observations, with a Review of the Literature. *Arch. Otolaryngol.*, 1940, 31: 626.

Since the superior laryngeal nerve runs through the piriform sinus and its course is superficial it is possible to produce anesthesia of the nerve by applying a local anest etic directly to the mucosa of the piriform sinus. This procedure is used by some laryngologists before operations on the larynx. In some cases of painful deglutition due to tuberculosis it is possible to block the nerve by the superficial injection of not more than 0.5 c.cm. of alcohol.

Acute inflammations localized in the piriform sinus are rare. In such cases the patients complain of severe pain on the affected side. On examination the rest of the pharynx, the nasopharynx, and even the larynx appear normal. Congenital cysts, the lining of which can also be seen in the piriform sinus, are likewise rare. However, since the piriform sinus forms a part of the posterior surface of the thyroid cartilage, it is possible for an abscess to form in the larynx from an isolated infection of the lymph tissue in the sinus if the inflammation has penetrated the interior of the larynx by way of the loose submucous tissue. In addition, the piriform sinus is the most dependent part of the hypopharynx and acts in a way as a receptacle for inflammations which may spread from the higher lying organs, such as the pharynx and the tonsils.

The anatomy of this region explains why inflammations in the piriform sinus do not always remain localized. Posteriorly and laterally the piriform sinus is in contact with the posterior surface of the pharynx. This in turn is bound to the prevertebral fascia by loose, movable connective tissue, rich in lymphatics. Thus there is a direct path for inflammation to spread to the mediastinum. The various ways in which abscesses of the posterior surface of the thyroid cartilage, particularly those of the piriform sinus, can invade the neighboring tissues of the neck and the mediastinum are:

1. Pus can spread from the piriform sinus along the posterior surface of the thyroid cartilage and, breaking through the cricothyroid ligament, reach laterally into the deep tissues of the neck. From here the pus can then follow the great vessels into the mediastinum.

2. Another path exists from the piriform sinus around the posterior edges of the thyroid cartilage into the region of the great vessels.

3. The abscess in the piriform sinus can break through the thyroid cartilage anteriorly without being definitely palpable or visible. This is due to its deep position behind the sternohyoid and sternothyroid muscles. In such cases the abscess may burrow downward and be imperceptible until later, after it has descended into the mediastinum. It may then appear as a painful swelling in the second intercostal space next to the sternum.

4. The fourth path leads from the piriform sinus into the neighboring prevertebral space, from which a direct path leads to the posterior mediastinum.

Foreign bodies are easily impacted in the piriform sinus. Pointed foreign bodies, such as needles and fish bones, may be buried beneath the soft mucous membrane through the act of swallowing and at times are therefore invisible on examination. In the author's experience, as well as that of others, frothing in the piriform sinus is noted in the following diseases, in all of which there is more or less disturbance in swallowing: esophageal diverticulum, aortic aneurysm, substernal thyroid, tumor of the esophagus, esophageal varices, and bulbar paralysis.

Finally, the following findings in an examination of the piriform sinus for possible malignant infiltrations should be considered: (1) deviation of the larynx to one side; (2) enlargement of the diseased piriform sinus; (3) shallowness of the piriform sinus through bulging of its floor; (4) hardening of the thyrohyoid membrane; and (5) the presence of small glands on and to the side of the thyrohyoid membrane.

NOAH D. FABRICANT, M.D.

Frank, I., and Lev, M.: Carcinosarcoma of the Larynx. *Ann. Otol., Rhinol. & Laryngol.*, 1940, 49: 113.

Since the time of Virchow various tumors have been described as carcinosarcomas or malignant tumors of dual origin. Recently, Saphir and Vass, and Saphir have reviewed the literature of these tumors. From this study, and from the study of a series of their own cases, they have grave doubt as to the existence of such tumors. Rather, they strongly suggest that in most cases of diagnosed carcinosarcoma, the tumors are actually carcinomas which had undergone morphological variations.

In order to study further the validity of this interpretation, the authors undertook to study a large series of carcinomas of the same organ in order to see how frequently morphological variations approaching the sarcomatous arrangement of cells occurred within carcinomas and how many so-called carcinosarcomas they could find in any one organ. The organ chosen for initial study was the larynx because of the frequency of origin of atypical carcinomas from the respiratory tract. Histological sections from 62 squamous and transitional cell carcinomas of the larynx were studied with the objective of analyzing the "sarcomatous" features in these tumors. It was found that almost half of the squamous and more than half of the transitional cell carcinomas showed this tendency to a variable degree. When it was found to be most marked, the tumors resembled what has been called carcinosarcoma.

Five cases of carcinosarcoma of the larynx found in the literature were reviewed, analyzed, and compared with the authors' proven carcinomas. They were found to be almost identical with their tumors, and, therefore, they are not carcinosarcomas but carcinomas which have undergone morphological variations.

The factors responsible for the sarcoma-like arrangement of cells are two: (1) an inherent tendency of the tumor itself, and (2) the amount of connective tissue environment of the tumor.

The question of the clinical significance of the "sarcomatous" features in these carcinomas is not definitely answered in the present study.

JOSEPH K. NARAT, M.D.

SURGERY OF THE NERVOUS SYSTEM

BRAIN AND ITS COVERINGS; CRANIAL NERVES

Bréhant, J.: Traumatic Diabetes Insipidus (Diabète insipide traumatique). *J. de chir.*, 1940, 55: 205.

The paucity of published reports concerning traumatic diabetes insipidus can hardly be taken as an index to the incidence of the disease, for, according to Bréhant, traumatic diabetes insipidus certainly cannot be regarded as rare or unusual, even though it is not of frequent occurrence. This is true especially in the present automobile age. To illustrate the syndrome, the author gives in full the history of a woman of forty-one years, who received a severe injury about the head with basilar frontal fractures, and who from the first day suffered a marked increase in thirst and urinary output. Blood-chemistry studies, urinalyses, and neurological examination gave normal findings save for a specific gravity of the urine equal to that of water. The output was from 10 to 14 liters a day, and the only agent which effected any control over the condition was nasal insufflation, 4 or 6 times daily, of powdered posterior pituitary lobe.

As to the cause of diabetes insipidus, the author points out that it may arise as the result of localized tumor in the floor of the third ventricle, syphilis, encephalitis, and other less specific factors. The traumatic type may be due (1) to tissue injury of the infundibular area as a result of fracture (clots within the third ventricle are believed to settle out on the floor of the ventricle and on the infundibulum); (2) to compression of the floor of the third ventricle resulting from a subarachnoidal hemorrhage; and (3) to sudden changes in the mechanics of the cerebrospinal fluid. Other causes may be hypophyseal and infundibular pressure from a callus; a localized osteitis; a localized pacchymeningitis; or a localized hypothalamic gliosis. The polyuria is believed to be the essential and primary symptom; it appears before the polydipsia; but although the polyuria is brought on through central control, these two symptoms appear to be dependent upon one another. The onset of the polyuria may occur immediately, within the first twenty-four hours after the accident, or it may occur as late as five weeks posttraumatically (Leriche and Fontaine). One can visualize certain of the afore-named pathological processes developing in this time interval, so that a delayed traumatic diabetes insipidus seems to be entirely possible. Other possible secondary or associated disturbances are (1) changes in the carbohydrate and fat metabolism, (2) changes in the sexual sphere, and (3) morphological changes such as nanism, acromegaly, and excessive emaciation. Disorders of sleep may accompany the condition.

Treatment is limited, but traumatic diabetes insipidus should not be looked upon as a disease existing beyond the pale of all hope. The surgical removal of a localized, extracerebral, subarachnoidal clot; repeated lumbar punctures; a salt-free regimen; and the intranasal administration of posterior pituitary-lobe powder have all been used successfully by many different investigators, and such measures should be given a fair trial when indicated. Occasionally traumatic diabetes insipidus is of only temporary existence; most commonly, however, it is permanent.

JOHN MARTIN, M.D

SPINAL CORD AND ITS COVERINGS

Aynesworth, K. H.: The Cervicobrachial Syndrome. *Ann. Surg.*, 1940, 111: 724.

The present study is based on 20 cases. Aynesworth is not satisfied with the designation "scalenus syndrome" for the syndromes produced by the scalenus anticus and cervical ribs. He prefers the term "cervicobrachial syndrome" as he believes that this term gives a comprehensive and anatomical concept which is accurate and inclusive. He divides his cases into those exhibiting neurological symptoms as their major manifestation; those which exhibit vascular symptoms; and those exhibiting a combination of both. He lists the following as the theories on the etiology of the cervicobrachial syndrome: (1) Compression of the nerve trunks as they pass between the scalenus anterior and scalenus medius. (2) Injury to the nerve trunks and the subclavian artery as they cross the normal rib or a cervical rib, or when they are obstructed between the clavicle and the normal or cervical rib. (3) Injuries to the sympathetic and vasomotor nerves supplying the subclavian artery by the scalenus anterior or cervical rib, producing vascular damage. (4) Traumatism, direct or indirect, of the scalenus-anterior muscle resulting in fibrosis and contraction, which compress the nerve trunks and the subclavian artery. (5) Embryological defects which alter the course of the nerve trunks in relation to the scalene muscles and normal cervical ribs. (6) Postural or functional defects, such as dropping of the shoulder girdle, posture due to ill health, faulty postural habits, occupational or vocational habits, advanced age. (7) Narrowing of the upper thoracic cap as a result of adjacent infections or anatomical defects. (8) Acute infections producing myositis. (9) Intermittent traumatism to the subclavian artery by a cervical or normal rib, due to normal movements of the shoulder joint.

In 80 per cent of the author's cases trauma was an etiological factor.

In the discussion Gage states that in 1934 he presented two prevailing theories: (1) Todd's failure of the descent of the shoulder girdle; and (2) Jones' low origin of the brachial plexus. To these two he added "spasm of the scalenus muscle" which he be-

lieves to be responsible for the persistence of the syndrome. He was able to confirm the spasm of the muscle as the cause for the persistence of the symptoms by blocking the scalenus-anticus muscle with 1 per cent novocain. This resulted in the relief of the symptoms for varying periods of time up to ten hours. In an anatomical study he found that there were a scalenus anticus major and minor in a number of subjects, the brachial plexus and subclavian artery passing between them in all cases in which they existed. To date this condition has been found in 8 of 27 cadavers. In 2 instances the brachial plexus was found to pass through the fibers of the scalenus-anticus muscle. These findings may have a bearing on the etiology of the scalenus-anticus syndrome. DAVID J. IMPASTATO, M.D.

Pennybacker, J.: Sciatica and the Intervertebral Disc. *Lancet*, 1940, 238: 771.

The syndrome of the intervertebral disc may be due either to a herniation of the annulus fibrosus on the posterior surface of the intervertebral disc, or to an actual rupture and extrusion of the nucleus pulposus. Usually a history of a definite back injury followed by persistent low back pain is obtainable, with an eventual "sciatica" and paresthesia in the area of sciatic distribution. There may be tenderness over the course of the sciatic nerve, slight muscular weakness in the foot and calf, and a diminished or absent ankle jerk. If the herniation is a large one there may be some increase in the protein content of the cerebrospinal fluid, though this finding is no more necessarily constant than is a partial manometric block. Lipiodol studies are usually concusive, and the herniated disc may be removed through a small, essentially unilateral laminectomy.

A common problem is the differentiation of intervertebral disc damage from low back pain, and sciatica due to various orthopedic causes, such as sacro-iliac strain, sacro-iliac arthritis, spinal osteoarthritis, scoliosis, and other structural changes. Low back pain and sciatica are common sequelæ of various pelvic and gynecological disorders, and there is the occasional perplexing, chronic, sciatic pain which, though not disabling, is persistent and annoying, and of which discovery of the causative factor is difficult. JOHN MARTIN, M.D.

Hyndman, O. R., and Jarvis, F. J.: Gastric Crisis of Tabes Dorsalis: Treatment by Anterior Chordotomy in 8 Cases. *Arch. Surg.*, 1940, 40: 997.

In their experience with 8 cases of gastric crises of tabes treated by chordotomy, the authors feel gratified with their results and urge the operation as a means of relief from this peculiar type of pain. The chordotomy must be bilateral and done at no lower a level than the third thoracic segment of the cord, the cutaneous loss of sensibility to pain being brought to the nipple line. They believe that the spinothalamic tracts lie farther anteriorward in the cord than is generally appreciated. An incision 3 mm. deep, beginning 2 mm. anterior to the dentate ligament and carried 3 mm. mesial to the anterior root, will section the tract completely in the upper thoracic cord.

Disadvantages of bilateral chordotomy are loss of cutaneous sensibility to pain and temperature, postoperative urinary retention, occasional motor weaknesses which are usually transitory, and loss of sexual potency. The beneficial results, including relief from both the pain and vomiting, always overshadow such minimal disadvantages.

JOHN MARTIN, M.D.

PERIPHERAL NERVES

Pozzan, A.: A Contribution to the Technique of Laterolateral Anastomosis of the Peripheral Nerves (Contributo alla tecnica dell' anastomosi latero-laterale dei nervi periferici). *Arch. ital. di chir.*, 1939, 57: 458.

Pozzan completes his report on laterolateral anastomosis of the tibial nerve with the previously sectioned peroneal nerve in young dogs, in which varying amounts of fibers of the tibial nerve were resected at the anastomotic site, while only the epineural and perineural sheaths of the peroneal nerve were removed; the involved nerves were examined at varying intervals. The following observations were made:

1. Simple incision of the epineurium and perineurium of the tibial nerve for a length of 15 mm. with resection of about one-twentieth of its fibers does not allow the muscles innervated by the peroneal nerve to recover their function or trophism even after eight months; histological examination of the nerve shows that the regenerated fibers do not exceed one-tenth of those previously present.

2. Removal of the epineurium and the perineurium and of one-twentieth of the fibers of the tibial nerve for a length of 15 mm., associated with a longitudinal incision 2 mm. deep in the nerve tissue and parallel to its fibers, does not allow functional or trophic recovery of the muscles innervated by the peroneal nerve even after eight months; histological examination of the nerve shows that the regenerated fibers are more numerous and amount to about one-eighth of those previously present.

3. Resection of one-fifteenth of the fibers of the tibial nerve shows after eight months a partial recovery of the function and trophism of the muscles innervated by the peroneal nerve; this nerve presents after two, five, and eight months a number of regenerated fibers equal to one-thirtieth, one-sixteenth, and one-sixth, respectively, of those found in controls.

4. Resection of one-eighth of the fibers of the tibial nerve is sufficient to allow nearly complete functional and trophic recovery of the muscles innervated by the peroneal nerve after eight months; this nerve presents an innervation 25 times lower than normal after two months and 4 times lower after eight months.

5. Resection of one-fifth of the fibers of the tibial nerve shows complete functional and anatomical recovery of the muscles innervated by the peroneal nerve after eight months; this nerve presents after two and eight months, one-twentieth and one-half, respectively, of the number of pre-existing fibers.

6. Resection of one-fifth of the fibers of the tibial nerve causes only partial and temporary signs of hypocinesis in the muscles innervated by this nerve; after eight months, these signs have disappeared and the histological sections are normal.

The histological study of the two nerves reveals that:

1. The changes in the sheaths of the tibial nerve above and below the anastomosis are only temporary and have disappeared within a few months.

2. The re-establishment of the nervous connections of the peroneal nerve does not change, at least within eight months, the anatomical condition (such as hypertrophy, sclerosis, and lipomatosis) of its epineural and perineural sheaths, which continue to appear somewhat like those of a partially regenerated nerve, even if regeneration of the fibers is subtotal.

3. The earliness of the systematization of the fibers in the anastomotic tract is proportionate to the number of bundles of fibers removed from the tibial nerve at its point of contact with the peroneal nerve.

4. It has been impossible to find in any histological section of the anastomotic tract deviations or real dislocations of the bundles of fibers, or of individual fibers, at any period or degree of the regenerative process; in fact, these fibers have not shown any signs of arrested or even difficult progression, such as terminal swelling or angulation.

RICHARD KEMEL, M.D.

Leriche, R.: The Reasons for Failure in Suture of the Peripheral Nerves (Des causes d'échec des sutures nerveuses). *Presse méd.*, Par., 1940, 48: 345.

Although suture of the peripheral nerves is generally regarded as a procedure which will lead to good results, this author believes that a large percentage of cases result in failure and are not reported. Even in the statistics of one individual, the results obtained for the suture of any particular nerve are extremely variable, ranging from a recovery rate of 15 per cent to one of 90 per cent for the radial nerve. The author is also of the opinion that there is a good deal too much attention drawn to the successful sutures.

He discusses the many factors which tend to lead to a satisfactory suture, including the vascular rôle, which is not generally understood. He is of the opinion that when a nerve is injured, for instance by violence such as a bullet wound, although the obvious lesion in the nerve is excised and the nerve repaired, there is still damage in the nerve itself, extending upward and downward for a distance from the site of the sympathetic lesion. Thus, the suture of such a nerve is doomed to complete or partial failure.

Fig. 1. Decalcification of the lower extremity of the radius, of the ulna, of the carpus, of the metacarpus, and of the first phalanges three months after section of the median nerve at the entrance of the carpal canal. The nerve was sutured immediately. It is to be noted that the rarefaction exists even above the level of the section.

Contrary to the opinion generally held in this country, he believes that the loss of more than 2 or 3 cm. of nerve substance will cause a poor result because of tension and traction on the nerve. This traction causes vascular changes in the nerve above and below the suture line, which prevent good healing. He reports 2 personal cases of primary nerve suture in a clear field in which the wounds healed by first intention, but the results obtained were not satisfactory.

Leriche believes that there is still occasion for treating large defects in the nerves by graft. He is impressed by the rôle of the sympathetic nervous system and its effect on the vascularity of the parts. He believes that the need of keeping up the vascularity of the parts in cases of peripheral nerve lesion by repeated procedures directed at the sympathetic system has been neglected.

The roentgenogram (Fig. 1) shows rarefaction in the bones of the hand and in the distal part of the radius and ulna in a lesion of the median nerve as it passed under the transverse carpal ligament. The nerve was treated by immediate suture. The picture was taken three months after the injury.

ADRIEN VERBRUGGHEN, M.D

SURGERY OF THE THORAX

CHEST WALL AND BREAST

Dahl-Iversen, E.: Cystic Disease; Its Pathogenesis, Prognosis, and Treatment (La maladie kystique, sa pathogénie, son pronostic et son traitement). *J. internat. de chir.*, 1940, 5: 85.

Dahl-Iversen reports 250 cases of cystic disease of the breast. This condition is characterized by the formation of numerous cysts of varying size in one or both breasts. The breast may not appear enlarged, but on palpation it is found to be nodular and of harder consistency than normal. The breast is often painful and the pain increases characteristically just before or during the menstrual period. A clear serous or sometimes turbid fluid may escape from the nipple under pressure or spontaneously in some cases. This fluid may be bloody in the absence of cancer. Microscopic examination of a cystic breast shows proliferation of the connective tissue and epithelium of varying degree; neoformation of the bile ducts and acini; and the formation of cysts, many of which are lined with a pale epithelium. The cells of this epithelium are higher than normal and have a fine granulated eosinophilic protoplasm. In some cases only a portion of one or both breasts is involved, the remaining tissue being entirely normal.

Both animal experiments and clinical experience indicate that cystic disease of the breast is due to ovarian dysfunction and interference with the normal balance of the ovarian secretions; but the exact nature of this dysfunction has not been definitely determined. Clinically, cystic disease of the breast develops either in the first years after puberty or, more commonly, in older women preceding the menopause. The author has found that the administration of corpus luteum does not relieve, but rather intensifies the symptoms, but the administration of folliculin has a favorable effect in a considerable percentage of cases.

The fact that cystic disease is sometimes found in association with carcinoma of the breast has led some investigators to conclude that malignant degeneration of the cystic tissues may occur with considerable frequency. The author's own experience and a review of the more recent literature has convinced him that this conclusion is erroneous. In his series of 250 cases of cystic disease which have been followed up for the last five years no sign of cancer of the breast has been found.

Of these 250 cases, 175, or approximately two-thirds, have been treated with folliculin; the usual dosage has been 2,000 I.U. given by mouth three times a day for three or four months, usually four. Immediately after this treatment, 88 per cent of the cases showed a marked improvement both objectively and subjectively; in the majority of this group the breasts were entirely normal in consistency on palpation; 8 per cent showed a less marked improvement, and 4 per cent no improvement. More than two-thirds of the cases treated with folliculin were re-examined more than three months after treatment was completed, on an average, two years after treatment. About half of the patients who had shown definite improvement had a recurrence of pain and infiltration of the breast. In most instances the recurrence had been noted a little more than three months after treatment; no recurrence was noted more than nine months after treatment. Another course of treatment with folliculin was less effective and the improvement was of shorter duration than after the first course. Approximately one-third of the patients treated with folliculin were free from symptoms from one to four years after treatment was completed. Others showed partial relief with little or no pain except for a few days before the menstrual periods. In some cases this pain was controlled by taking from 1 to 3 tablets of folliculin daily (2,000 I.U. each) during the week preceding menstruation.

In cases in which operation was necessary, resection of the involved tissue was done if the lesion was localized; in other cases the breast was removed with conservation of the skin and nipple. The removed tissue should always be examined microscopically and if any evidence of beginning malignancy is found, a radical operation should be done as soon as possible. ALICE M. MEYERS.

Cramer, W.: The Hormonal Etiology of Breast Cancer. *Am. J. Cancer*, 1940, 38: 463.

The experimental production of mammary cancer by estrogenic hormones is one of the landmarks in the investigation of cancer. The importance of this discovery lies in the fact that the carcinogenic agent in this instance is a substance normally produced in the body and possessing definite physiological functions, in fact, a hormone. This adds to our knowledge of the etiology of cancer a new conception, namely, that for at least one organ, the breast, all the etiological factors concerned in carcinogenesis may be normally present in the organism.

Even if the estrogens have a direct carcinogenic effect, it does not manifest itself until they have produced their physiological effect on the breast. This physiological effect is, like other hormonal effects, subject to control. We have thus, perhaps for the first time, the hopeful indication that a prophylaxis of mammary cancer by medical treatment is a reasonable possibility.

The most obvious possibility is that mammary cancer appears as a result of a hypersecretion of this hormone. However, observations on high-cancer strains failed to give any evidence of this. We must assume, therefore, that the carcinogenic effect of estrogens is limited by factors inherent in the animal. We call these factors "susceptibility." For the

etiology of spontaneous skin cancer, the presence of the carcinogenic agent (a substance foreign to the physiological economy of the organism) is of decisive importance. For the etiology of spontaneous mammary cancer, in which the carcinogenic agent is a hormone normally formed by the body and always present, the factor of susceptibility is of greatest etiological importance. There are certain organs for which the cancer incidence is governed largely by an inherited constitutional factor. The outstanding organs in this group are: the breast and the uterus in women, and probably the prostate in man. There is another group of organs in which the incidence is governed either by the occupation or by social conditions, so that we have what may be called "social cancer." These organs are those exposed to the influences and stimuli coming from without; they include the skin, and the digestive tract, from the lips to the stomach, inclusive.

With regard to the breast, the experiments carried out by Horning and the author give some evidence that susceptibility is dependent on the functional activity of the endocrine system, that is, upon a factor outside the breast. It was found that the action of estrogenic hormones is not limited to the female sex organs, but extends to the whole endocrine system, the organs most prominently affected being the pituitary body and the adrenal glands. The changes affect almost exclusively the anterior part of the pituitary body.

It was found that following adrenalectomy the general physiological effects of estrogens, such as arrest of growth, emaciation, and testicular atrophy, are diminished. Development of the breast in response to estrogens was also impaired, and carcinogenesis was either delayed or prevented. The physiological effects of the ovarian estrogen are conditioned by at least two other hormones, one from the anterior pituitary lobe, which antagonizes the estrogen, and one from the adrenal cortex, which enhances the action of the estrogen. The adrenal medulla contains probably a third conditioning factor, which, like the thyrotropic hormone, inhibits the action of estrogens. This relationship extends to the physiological action on the mammary gland, which responds to the estrogen by epithelial proliferation, less vigorously if the animal has been either completely adrenalectomized or thyrotropinized, and also, within limits, to the development of cancer in the breast.

The author draws the following conclusions concerning the susceptibility to mammary cancer:

1. It is not a fixed and unalterable quality residing within the organism, but can be modified.

2. It does not reside entirely, if at all, within the breast.

3. It is conditioned partly by a disturbance of the endocrine balance.

From the point of view of human cancerology, the conception of an endocrine imbalance as an etiological factor in cancer of the breast, and probably also of the uterus, should serve as a useful guide for clinical investigations. There is now a possibility of treating precancerous conditions of these two organs by appropriate hormones. JOSEPH K. NARAT, M.D.

ESOPHAGUS AND MEDIASTINUM

Gerlings, P. G.: Disorders of the Mouth of the Esophagus in the Syndrome of Plummer and Vinson (Dysphagia with Anemia). *J. Laryngol. & Otol.*, 1940, 55: 143.

Dysphagia associated with a hypochromic anemia (the so-called Plummer-Vinson syndrome) usually occurs in middle-aged women. Dysphagia usually has been present for years, and necessitates nourishment with liquids or soft foods. The discomfort resulting from the dysphagia is usually localized at the level of the larynx. On examination one usually finds a small mouth with fissures in both corners. Teeth are usually absent and the buccal mucous membrane is pale. The tongue appears glossy and the papillæ atrophic. Leucoplakia may be present. The pharyngeal reflexes may be diminished. Koilonychia (spoon nails) are often seen.

The blood picture is that of hypochromic anemia and shows no other abnormalities. Achlorhydria is frequently found, and the anemia responds surprisingly well to the administration of iron, and, if necessary, hydrochloric acid.

On roentgenographic examination stagnation in the valleculæ glosso-epiglotticæ and in the sinus piriformis is often seen. The cause of this stagnation is thought to be due either to a partial swallowing paralysis or else to a reduced sensitiveness of the mucosa of the hypopharynx. Roentgenographic examination may reveal also a stagnation just above the mouth of the esophagus, or there may be a spastic stricture just below the mouth of the esophagus, probably due to spasm resulting from a fissure. Cicatricial stenosis of the mouth of the esophagus or of the esophagus itself may occur and may be seen on roentgen examination. Roentgenological examination should therefore always be performed before instrumentation of the esophagus be attempted.

Esophagoscopy may show fissures, leucoplakia, or extensive erosion of the mucosa in the upper part of the esophagus. These lesions may cause spasm, cicatricial stenosis, or even esophageal carcinoma.

A controversy still exists as to the reason for the atrophic changes of the skin, mucous membranes, and nails. It is thought that iron deficiency and inadequate diet are responsible for these lesions. Frequently, all symptoms disappear upon simple treatment of the mouth of the esophagus with a bougie.

The author presents 6 cases of the Plummer-Vinson syndrome, together with excellent roentgenographic reproductions. LUTHER H. WOLFF, M.D.

Toellner, H. M.: A Contribution to the Pathology of Esophagitis (Beitrag zur Pathologie der Oesophagitis). Jena: Dissertation, 1939.

On the basis of cases described in the literature, and 7 of the author's own cases, which he was able to

follow clinically and post mortem, this contribution is made to the pathology of esophagitis.

A sixty-five-year-old woman, who had suffered from attacks of vomiting for forty-five years, died eighteen days after removal of a perforated gall bladder. At autopsy, the esophageal mucosa was found to be thickened and thrown into longitudinal folds. An eight-year-old girl died of sepsis following osteomyelitis of the thigh. Her esophagus showed marked folding of the mucosa with numerous superficial ulcers vertically arranged. An eighty-one-year-old woman with clouded consciousness vomited frequently. In the mucous membrane of the esophagus there were numerous mucus and pus cysts, also frequently in the long axis. The next 2 cases presented acute disturbances of consciousness from accidents; in both, there were mucosal defects in the lowermost portion of the esophagus. In the last 2 cases the patients died of carcinoma of the colon; they showed severe inflammatory changes in the esophagus, marked fold formation, and occasional ulcers.

From these findings, it is seen that esophageal damage is not a disease entity, but is produced by the underlying disease. In all cases, there is disturbance of consciousness and, frequently, there is vomiting. These conditions are due to disease of the digestive organs or to a lesion of the central nervous system. For correct interpretation of the pathological changes found in the esophagus, two observations must be thought of:

1. The stomach attempts to heal existing gastritis by forming mucosal folds, so that portions of the mucosa are protected from the effect of the gastric juice.

2. Complete interruption of the vagus nerve causes relaxation of the esophageal musculature and spastic contraction of the cardia, whereas stimulation increases the tonus of the musculature and relaxes the tone of the cardia and the cardial esophagus. The esophagus responds to stimulation by longitudinal fold formation: the cardia is opened, and gastric juice flows into the esophagus. There are no primary disturbances of the esophageal mucosa, aside from malformations, corrosions, or trauma.

(Salzer). Leo M. Zimmerman, M.D.

Wachs, E.: The Methods and Results of Treatment of Cardiospasm (Ueber Methoden der Kardiospasmusbehandlung und ihre Erfolge). *64 Tag. d. deutsch. Ges. f. Chir.*, Berlin, 1940.

In Fromme's Clinic a total of 52 patients (31 women and 21 men) were treated during the last sixteen years by various methods for cardiotonic esophageal dilatation. The former purely surgical treatment was replaced by the bloodless Starck sound dilatation method because of the excellent results obtained by the latter procedure. The treatment of choice to date remains the bloodless sound dilatation, which is one of the most useful procedures and, therefore, is entitled to first place as the most justifiable method for treating cardiospasm. Only after failure of the dilatation method due to cicatricial stenosis, or to the impossibility of introducing the cardiodilators through markedly sinuous or diverticulous indentations of the esophagus, are operative interferences indicated. Sixteen patients were treated operatively: 1 by a temporary gastrostomy as an emergency operation; 2 by Heller cardiomyotomy; 4 by cardioplasty; and 9 by Heyrovsky gastro-esophageal anastomosis. The last-named method unquestionably yielded the best results, anatomically and functionally. All these patients (the operations were undertaken in 1 patient fourteen years ago; in 3, eleven years ago; in another 3, ten years ago, and in 1 a little over one year ago) remained symptom-free and able to work. None of them ever had return of the dysphagia.

The roentgen re-examinations also revealed a permamency of the dilated esophagus without any tendency toward contractions, thus proving this as the best method for assuring a nearly normal organ. Good results may also be obtained by the Heller cardiomyotomy. It is striking, however, to note reports of a comparatively high rate of recurrences following the Heller operation in the literature. The results of the plastic operations were not especially favorable, functionally nor anatomically. All of the patients retained deglutitional annoyances: their roentgen reports showed the esophageal dilatation nearly unaltered and a great expansion of the same still in evidence. Twenty-six patients, whose ages ranged from seventeen to fifty-eight years, were treated with the Starck inflexible dilator. The results were very good, even excellent, in 14 patients. These patients have absolutely no dysphagia symptoms and are really cured. The cures apparently lasted six years in 2 of these patients, five years in 3, four years in 3 others, four years in 2 patients, and two years in 2 other patients. The results of the dilatation method in 10 patients were good without a doubt. However, these patients complain of an occasional dysphagia, but remain able to work and do not show any signs of nutritional disturbances. It is acknowledged that following the bloodless dilatations, the expanded esophagus does not shrink materially in some patients, yet this treatment left the patients entirely free from all symptoms of dysphagia.

However, if the cure following the dilatation method is judged by the roentgen plates, the results would not be so favorable. In some of the patients the esophagus resumed a nearly normal contour after bloodless dilatation of the cardia. No unfavorable result after dilatation treatment was ever observed in the clinic; but 2 patients that were treated before entering our service were lost because of perforation of the esophagus by a consequent mediastinitis. Occasionally ruptures of the esophagus resulting from the bloodless dilatation treatment were reported; therefore, this treatment should not be classified as non-hazardous even though the danger is practically minimal when compared with the dangers of operative procedures.

In the discussion MARTIN was glad to note that after doctors treated cardiospasm with all the various surgical methods, the author's report established the fact that a return to the dilatation sound method is again the vogue. Martin recommended this method for forty years, during which time he has employed it in numerous patients and obtained good and lasting results (*Mitt. a.d. Grenzgeb. d. Chir. und inn. Med.* 1900). It made no difference to him whether the dilatation sound of Gottstein or of Starck was used, the result was essentially the same. Both are good.

In the more unusual cases in which the small sounds cannot be forced through the esophagus a gastrostomy is done to maintain nourishment; then the employment of fine buckshot and thread, according to Von Hacker's method of sounds, is resorted to *ad infinitum*. As soon as a noticeable dilatation has been forced, the dilatation from pharyngo-esophageal entrance with sounds is undertaken and continued until a maximal expansion is obtained. This returns the function of deglutition to the normal status, and it will remain normal if the sound treatment is repeated at regular intervals; this will also prevent the appearance of stenosis. Prevention of stenosis is the main issue as this means no recurrences. This positive statement is supported on the basis of his very numerous successful experiences. Only in the most unusually exceptional cases one of the complicated operative methods was found to be necessary. Martin had very fortunate results with dilatation treatment.

ANSCHUETZ found no lasting results with the endless sound dilatations. Dilating with the fingers was given up by Mikulicz in favor of the Gottstein sounds. Even this is not sufficient in some cases; according to the anatomical location, muscle-splitting or anastomosis must be done. Unfortunately Anschuetz had no experience with suggestion therapy. Two cases of polyspasm were reported by Anschuetz; the pylorospasm developed after gastrostomies, with suspension of the gastro-enterostomy function and after the introduction of a tube into the lower bowel enterospasm occurred. The patients then died.

One case, that of a young girl, twenty-two years old, with cardiospasm, and another case, that of a woman, forty-two years old, with esophogeal ulcer, were reported by Frey and Plenk, respectively. No information was obtained by section, and there was no evidence of peritonitis.

(E. WACHS). MATHIAS J. SEIFERT, M.D.

MISCELLANEOUS

Bergenfeldt, E.: A Contribution to the Knowledge of Diaphragmatic Hernia (Ein Beitrag zur Kenntnis des Zwerchfellbruches). *Acta chirurg. Scand.*, 1940, 83: 519.

After discussing the embryology and anatomy of the diaphragm, the author proposes to classify diaphragmatic hernias into three groups:

1. Congenital
2. Acquired non-traumatic
3. Acquired traumatic

In all the groups true hernias (with sac) and false (without sac) may be found. As congenital diaphragmatic hernias often remain symptomless for years, it may be difficult to decide whether or not such hernias are congenital in adults. The author reports the following 3 cases:

Case 1. A boy of one and one-half years had suffered from various gastric complaints since the age of three months. Six weeks before this writing he had hematemesis (about 3 teacups of blood). An x-ray examination revealed a normal esophagus, but there appeared a "bubble" in the chest, which was clearly identified as a part of the stomach which had been displaced into the thorax through a para-esophageal hiatus hernia. This roentgen diagnosis was affirmed by operation. Through an upper median laparotomy with resection of the end of the sternum the stomach was pulled down into the abdomen and the hiatus opening was closed with catgut sutures. The recovery was uneventful, and an x-ray check-up before discharge and follow-up examinations when the patient was two and one-half and three and one-half years old showed normal findings. The patient has not had any of his former complaints since the operation.

Åkerlund differentiates pathologically the following forms of hiatus hernia:

1. Hernias with congenital shortening of the esophagus. In this type the distal part of the esophagus has not descended through the diaphragm. As no effective surgical treatment is possible, these hernias are of but little practical interest.

2. Para-esophageal hernias, in which the stomach or any other abdominal organ, after normal descent of the cardia, has ascended aside of the esophagus.

3. The so-called acquired hiatus hernias, in which the distal part of the esophagus, after normal descent, has ascended with adjoining parts of the stomach into the thorax.

The author's first case obviously belonged to Group 2.

Case 2. A boy of four years had had an attack of violent pains in the whole abdomen with vomiting when he was three. Three days before admission, another such attack with incessant vomiting and pain had begun and had persisted. There had been no bowel movement. On admission there was no meteorism, and the abdomen was rather negative. The heart was found displaced to the right, the anterior wall on the left side of the chest revealed distention, and the breathing sounds were missing. Intestinal sounds were audible. Roentgen examination revealed the presence of a part of the colon in the left chest; it was full of gas and revealed fluid levels.

An intercostal incision was made in the left seventh interspace with wide opening of the thorax. The left pleural cavity was almost entirely filled with intestine. In the apex was the lienal flexure

with the spleen. In addition, about half of all the small intestinal loops and the transverse and the descending colon were in the chest. There was no peritoneal covering forming a hernial sac. The opening of the hernia was about 3 cm. in diameter in the posterior lateral part of the diaphragm. Reposition could not be done without enlargement of the opening. There were no marked strangulation rings on the intestines. The opening was closed, and because of weakness of the muscle layer, closure was difficult and had to be accomplished partially by obliteration of the complementary space with sutures. Recovery was eventful with chicken pox, wound suppuration and pleural exudation, mastoiditis, and erysipelas of the face. Finally recovery took place. X-ray check-up showed normal findings, as did a follow-up examination after one year. Undoubtedly, this had been a congenital hernia.

Case 3. A woman of forty-nine years had had stomach complaints from her fifteenth to her thirtieth year. In 1913 she had been operated upon for adenomatous goiter. In 1934 there were recurrence of the goiter and hoarseness. Lately she had had anginal symptoms. On admission in August, 1938, she was found to be very fat with a slight decompensation. On the left there were dullness and diminished breathing sounds. Roentgen examination of the intestinal tract, by means of barium-enema displacement of the lienal flexure into the left chest and contrast meal, showed the stomach to be rotated and displaced into the left chest where it lay behind the colon. In view of the general condition of this patient operation was not believed to be indicated. This case showed that a diaphragmatic hernia can be latent for some period of time.

As to symptomatology, diaphragmatic hernias usually are not diagnosed without x-ray studies; they are suggested by the combination of abdominal and thoracic signs and symptoms which they produce. The most frequent abdominal symptoms are pains, localized in the epigastrium or in the left upper abdomen. If the stomach is herniated, stomach symptoms prevail. If the intestines form the content of the hernia, the symptoms will be determined chiefly by the impaired passage, and an ileus-like picture will develop. The thoracic symptoms are pain, oppression, dyspnea, cyanosis, angina pectoris, and coughing spells. Dextrocardia is an important objective sign in hernias of the left side and percussory changes and auscultatory findings often accompany them. Typical intestinal sounds heard over the chest are significant, especially when in the upper half of the chest where transmission from the abdomen is impossible.

Effective treatment is obtained by surgery only. However, surgery is limited to Åkerlund's second group of cases. In the first group, the congenitally shortened esophagus prohibits operation, and in the third, there is very often no major discomfort. The latter group occurs chiefly in senile people. Incarceration, of course, is always an absolute indication. Younger people probably should always be operated on when the diagnosis is made. In older people only major discomfort justifies an intervention. The author's third case demonstrates the importance of early diagnosis. If the condition had been diagnosed between the fifteenth and thirtieth years, the general condition would have permitted an operation; however an operation could not be done on recurrence of the symptoms at the age of forty-nine. In early infancy conservative treatment is justified as diaphragmatic hernia in infants may heal spontaneously.

As to the operative procedure, some authors choose thoracotomy and others laparotomy, while the majority make individual decisions according to the location of the opening. While surgeons in general might be inclined to consider the laparotomy route as less dangerous, this is not borne out by the statistics of Hedblom who found in 378 cases a mortality of 19.8 per cent following thoracotomy and a mortality of 22.3 per cent following laparotomy.

HEINRICH LAMM, M.D.

SURGERY OF THE ABDOMEN

ABDOMINAL WALL AND PERITONEUM

Uggeri, C.: Hernias of Epiploic Appendices and Their Complications (Le ernie di appendici epiploiche e le loro complicanze). *Ann. ital. di chir.*, 1940, 19: 215.

Uggeri recalls the anatomy of epiploic appendices and points out that at times they contain an intestinal diverticulum. Their morbid complications consist of mechanical impediment to the circulation by direct pressure or torsion, infection, and adhesions which may lead to intestinal obstruction. Epiploic appendices may penetrate into a hernial sac. This occurs more frequently on the left side, in males, and in advanced age, and depends on the number, volume, and form of the appendices and on the degree of mobility and ptosis of the intestine, especially the sigmoid colon. Hernia of epiploic appendices is rather frequent and gives rise to complications in a large percentage of the cases. The author reports 9 cases, 6 of which were complicated by strangulation or torsion. The appendices, especially in case of torsion, often contract adhesions of their distal extremity with the hernial sac, because of the continuous irritation caused by their backward and forward movement in the sac. They may be transformed into fibrous cords and their pedicle may become long and thin and even rupture, a foreign body being left inside the hernial sac. In recent cases, the changes found were those of strangulated epiploon. Usually, the amount of fluid in the hernial sac is small and may be serosanguineous or seropurulent.

Hernial epiploic appendices may give rise to various complications of which the author presents examples taken from the literature. Simple strangulation occurs mostly in old, irreducible, and well tolerated hernias, but it may also be the first sign of a hernia. Pain is the principal symptom: it is felt in the hernia and radiates to the abdomen or the umbilicus; the general condition is always good. In most cases, there are no symptoms of obstruction. Intrahernial torsion presents the same symptomatology, but at times there are temporary attacks of pain which precede the appearance of the final syndrome and which are interpreted as abortive phenomena of torsion. The torsion is nearly always single, even if several epiploic appendices are present in the hernial sac; its mechanism is still unknown. Torsion is often accompanied by strangulation and then occurs first. Intrahernial foreign bodies are an operative finding and originate through destruction of the pedicle of an epiploic appendix, especially in the subacute form of torsion. The adhesions contracted by the distal part ensure its nutrition and prevent its necrosis. Geniculation with adhesion of the sigmoid to the hernial opening has been reported in case of incarceration of an epiploic appendix and may give rise to symptoms of intestinal obstruction. Hernial diverticulitis has been described in 1 case only.

If left alone, the complications of hernial epiploic appendices may gradually become worse until an urgent intervention is found necessary, or they may improve gradually and disappear completely. It is best to intervene as soon as possible in all cases; the result of the operation is practically always good. Hernial diverticulitis seems to be the most unfavorable complication; probably the only instance of death was caused by diverticulitis. The treatment is that of any hernial strangulation. Simple reduction into the abdomen of a strangulated or twisted epiploic appendix is to be condemned. Ligation of the pedicle and resection of the appendix, cauterization in case of doubt as to whether a diverticulum has been opened, and, eventually, burial of the stump are recommended. Radical treatment of the hernia is done at the same time, except in clearly infected cases. RICHARD KEMEL, M.D.

Coenen, H.: Gas Peritonitis (Die Gasperitonitis). *Zentralbl. f. Chir.*, 1939, p. 5221.

Coenen collected the records of 75 cases of gas or air peritonitis and attempted to determine the causes. The clinical picture he reports develops slowly with gradually increasing pain and a collection of gas in the peritoneal cavity which causes a widening of the costal arch, decreased liver dullness, and labored breathing. Peristalsis is preserved. Signs of peritoneal infection are absent early but may appear later. If the abdomen is opened, a large amount of odorless gas escapes explosively. The intestines are pressed together. In 39 cases smooth healing was observed; 28 patients died later of peritoneal infection.

In 32 cases the gas in the peritoneal cavity was caused by a ruptured peptic ulcer. The reason that the gas which leaks into this cavity does not cause an infection can be one of two. One is that a closed valve is produced by the liver or some other viscus which is pressed against the opening by the gas. The other reason is that the infection might be prevented by the acid gastric secretion while the gas is permitted to rise to the diaphragm. Graumann has recently reported 7 silent gastric perforations, all of which healed without surgical intervention. A similar picture may also develop from perforation of the small bowel either by a perforating injury as described by Nini and deMassie, or from an infection such as tuberculosis or typhoid. Fifteen cases of pneumoperitoneum caused by perforation of the large bowel were collected by Coenen. Two of these were caused by perforation of diverticula. Of interest are several cases of pneumoperitoneum which developed through injury of the abdominal wall in which atmospheric air was admitted through a

valvular mechanism. These cases must be differentiated from pneumoperitoneum by gas formation. Loehr's studies showed that the specific gas-producing bacteria never develop gas in the abdomen. Because of this evidence and because intestinal perforation is difficult to demonstrate in infants at necropsy, it is difficult to accept Obadalek's explanation of his case of genuine gas peritonitis in an infant. Of course, the aerobic bacilli coli can produce gas in the abdominal cavity, but this is foul smelling whereas the gas of pneumoperitoneum is odorless.

The treatment of pneumoperitoneum is quite clear. If pneumoperitoneum with peritoneal infection is present, the surgeon must find the cause and close off the gastric or intestinal opening, as the case may be. RULON W. RAWSON, M.D.

GASTRO-INTESTINAL TRACT

Martini, T., Bianchi, A. E., Oliver, G. G., and Wybert, A.: The Diagnosis and Treatment of Profuse Gastro-Intestinal Hemorrhages (Diagnóstico y tratamiento de las grandes hemorragias gastro-intestinales). *Rev. Asoc. med. argent.*, 1940, 54: 239.

The authors discuss the treatment of grave gastro-intestinal hemorrhages caused by intrinsic lesions as well as by certain infectious diseases, toxic conditions, and other pathological processes responsible for a hemorrhagic diathesis.

Before any therapeutic measure is considered, a definite diagnosis should be made, particular attention being paid to extradigestive conditions, such as lesions of the spleen or liver, cholelithiasis, acute or chronic pancreatitis, leucemia, hemophilia, uremia, and septicemia. The examination should include determinations of the urea and sugar content of the blood. Gastro-intestinal lesions leading to profuse hemorrhages may be divided into four groups: (1) local changes caused by tumors or ulcers; (2) post-operative local changes; (3) cryptogenetic conditions, i.e., those of an obscure origin; and (4) hemorrhagic colitis, caused by polyps, tumors, diverticulitis, and appendicitis.

In the conservative treatment blood transfusion occupies the main place; the mechanism of its effect is manifold: it increases the tonus of the blood vessels, acts as a substitute for the lost blood, mobilizes stored blood, stimulates the hemopoietic system, re-establishes the acid-base equilibrium, displays a hemostatic, bactericidal, and antitoxic effect, and has a certain value from the viewpoint of organotherapy.

Conservative treatment is recommended by the authors for acute hemorrhages caused by gastric or duodenal ulcers, while chronic, recurrent bleeding responsible for secondary anemia is considered an absolute indication for an operation to be performed under local anesthesia after a preceding blood transfusion. Partial gastric resection is recommended by the authors.

Thrombocytopenic purpura, primary thrombophlebitic splenomegaly, and splenic anemia are best treated by splenectomy.

Diverticulitis responsible for grave hemorrhages calls for a resection of the involved segment.

JOSEPH K. NARAT, M.D.

Kaump, D. H., and Parsons, J. C.: Extrarenal Azotemia in Gastro-Intestinal Hemorrhage: (1) General and Clinical Consideration; (2) Experimental Observations. *Am. J. Digest. Dis.*, 1940, 7: 189, 191.

In recent years azotemia has been found in a number of disease states for which no renal lesion can be demonstrated. The authors became interested in that form of extrarenal azotemia associated with gastro-intestinal hemorrhage because of a case of bleeding peptic ulcer which came under their observation.

On admission to the hospital, the patient's blood urea was 90 mgm. per cent, and this gradually dropped to normal over a period of ten days. The authors were impressed by the urinary excretion of chlorides which was exceedingly low (about 30 mgm. per cent of sodium chloride) in spite of an adequate volume output of urine (from 1,200 to 1,900 c.cm. per day). The blood urea returned to normal before the plasma chlorides or the urinary chlorides began to show any significant rise. The authors believed this to be an indication that the blood-chloride concentration *per se* has little to do with the elevation of the blood urea. A number of possible explanations for the elevated blood urea are found in the literature: bacterial decomposition of blood lying in the intestine, increased protein catabolism, impaired renal function *per se* or associated with lowered blood pressure due to blood loss, and certain other conditions.

The authors produced extrarenal azotemia in dogs by removing blood from the heart and placing it in the gastro-intestinal tract with a stomach tube. This was characterized by two rises in the blood-urea value, the first from twelve to twenty-four hours, and the second from forty-two to forty-eight hours, after the beginning of the experiment. When fasting and non-fasting animals were used, and when one group lost blood only and the other was fed blood only, this double curve could be dissociated into its two component factors. Thus, the initial rise was produced by the feeding of the blood and the secondary rise was due to the loss of blood. Both elevated values (maximum, 30 per cent above normal) fell within a few hours and both were accentuated if food of a high protein content was given. Plasma-chloride and urea-ratio determination values were not significantly altered in any of the experiments. Hypochloremia, hemoconcentration, and dehydration played no significant rôle in this form of extrarenal azotemia. The rise in blood urea was due to several factors: (1) the assimilation of the ingested protein and digestion products of the whole blood in the gastro-intestinal tract, and (2) an increase in protein catabolism. In no instance did an animal assume the clinical picture of uremia.

AUGUST JONAS, JR., M.D.

De Vincentiis, A.: Experimental Gastric and Intestinal Mycosis (Micosi gastriche ed intestinali sperimentali). *Clin. chir.*, 1940, 16: 205.

The author briefly reviews the subject of primary mycotic infections of the digestive tract and particularly of the stomach. Primary gastric actinomycosis is a rare disease. The first case was reported by Israel in 1888. Other cases were subsequently reported by Grill in 1895, Prutz in 1897, Duckworth in 1900, Robinson in 1911, Pohl in 1912, Hadjipetros in 1925, Zuckschwerdt and Eck in 1932, and Strawinsky in 1936. The lesions are characterized by ulcerative necrotic hemorrhage and, in some cases, by granulation tumors and fistula formation. It is generally agreed that the infection enters through the mouth. It may be caused by the ingestion of infected meat, by carious teeth, or by secretions of pulmonary foci. Means of spread to the stomach or intestine are by direct extension from neighboring foci or, rarely, by the blood stream.

Experimental observations on gastric actinomycosis are rare. These are briefly reviewed by the author. He states that Lichtheim reproduced the lesions in rabbits.

The author performed a series of experiments on rabbits to establish that growth of fungi in the gastric and intestinal regions was possible and to determine the easiest means of growth and the anatomicopathological alterations. The fungi employed were myocotrula albicans, sporatrichum bermanni, and actinomyces albus. The experiments were divided into three groups, each containing 12 animals. In Group I, ½ c.cm. of the fungus solution was injected with a fine needle into the gastric and intestinal wall. In some of the animals of Group II ½ c.cm. of the solution was injected into the gastric and right or left epiploic arteries, and in the others into the superior and inferior mesenteric arteries. In Group III the fungus was given the animals by mouth for nine days by placing it on cabbage leaves which were eaten. A gastrostomy or enterostomy was also done and excoriations of the mucosa were made with the needle. All the animals were killed ten, twenty, thirty, forty, sixty, or eighty days after inoculation.

The experiment on each rabbit is reported in detail. It was found that the lesion was most difficult to reproduce when the fungus was introduced by mouth (2 of 6 gastric and 1 of 6 intestinal lesions), whereas intramural inoculation was easiest (10 of 12 gastric lesions).

The lesions produced in the stomach and intestine had a hyperplastic granulomatous character. The center of the lesions contained necrotic substances and fungous elements mixed with polymorphonuclei and mononuclei. Surrounding this center was a layer of leucocytic infiltration containing epithelial and histiocytic cells. More peripherally there was considerable connective tissue with numerous fibroblasts and newly-formed vessels. The degree of connective-tissue formation varied proportionately with the period of time after inoculation.

From these observations the author concludes that the stomach and intestine are organs which can be infected by fungi, that the easiest means of infection is by submucous or endo-arterial inoculation, and that the lesions produced are characterized by a granulomatous hyperplasia with a tendency toward encapsulation and perhaps toward spontaneous resolution. MICHAEL DEBAKEY, M.D.

Mann, W. N., Sundberg, S., and Herbert, W. E.: Cancer of the Stomach in London, in Stockholm, and in Amsterdam. *Guy's Hosp. Rep.*, Lond., 1939, 89: 274.

The object of the present investigation was to compare the frequency of cancer of the stomach in comparable groups of patients in London and in Stockholm, and then, by comparing the habits and dental conditions of this same group, to determine whether any factors exist in those habits which might be favorable to the development of cancer of the stomach.

The total incidence of cancer in all European races and in the various social divisions of those races is remarkably constant. It was amply demonstrated that cancer of the stomach is more than twice as common in Sweden and in Holland as it is in England. The figures indicating the masticatory surface show that the Dutch are superior to the English in this respect, while the Swedish are far worse. Gross oral sepsis, on the other hand, is much more common in the Dutch and Swedish groups than in the English. It may be observed here that a relationship between oral sepsis and frequency of cancer of the stomach is seen in England when the incidence is analyzed according to social classes. The poorer classes have a greater degree of oral sepsis and a higher incidence of gastric cancer than the well-to-do. No conclusion can be drawn about the importance of the temperature at which food and drink are taken nor about the use of tobacco.

The importance of the extrinsic factor in the development of new growth is discussed with special reference to the incidence of cancer of the stomach in various European countries. JOHN W. NUZUM, M.D.

McClure, R. D., and Fallis, L. S.: Partial Gastrectomy: A Consideration of Certain Technical Problems. *Ann. Surg.*, 1940, 111: 743.

The mortality of subtotal gastrectomy for peptic ulcer in the authors' clinic for a fifteen-year period was 10 per cent, and for the last five years 5 per cent. In the last consecutive 53 cases there was but 1 death. The most important factor in this falling mortality has been the increasing experience of the operators which resulted in several improvements in technique; these are discussed in detail. Important points in pre-operative preparation are care that the hemoglobin is at least 70 per cent, attention to dental prophylaxis, refusal to operate within six weeks of an upper respiratory infection, repeated lavage of the stomach with bicarbonate of soda solution in the two days before operation, final pre-operative lavage

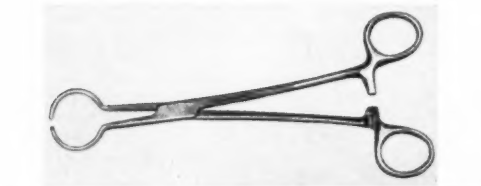

Fig. 1. The ring clamp for applying traction to the duodenum.

Fig. 2. The modified Furniss clamp with its detachable handle.

Fig. 3. Duodenum just before sectioning. The McClure modification of the Furniss clamp is shown in place, with the ring clamp just proximal to the pylorus.
(Courtesy of J. B. Lippincott Co.)

with half-strength hexyl-chlorometa-cresol (200 c.cm. being left in the stomach), and repeated enemas to cleanse the colon. The anesthetic of choice is spinal nupercaine administered by the Jones method. Sedation is accomplished by means of seconal (3 gr.) and morphine sulfate (¼ gr.). Blood pressure is maintained by the administration of 600 c.cm. of 10 per cent glucose followed by 600 c.cm. of citrated blood. A midline incision is used.

The duodenum is mobilized, after cutting the right gastric artery, with the aid of a special ring clamp which encircles the prepyloric area as a retractor. It is sectioned distal to the ulcer if this is possible without encroachment on the common bile duct or the papilla of Vater. If this is not possible, as may occasionally be ascertained only after opening of the duodenum, the section is made through the ulcer or proximal to it, as circumstances indicate. Closure of the duodenal stump is then made with the aid of a modified Furniss clamp, which is furnished with a detachable handle and is easily manageable in a deep wound. A purse-string suture, interrupted Lembert sutures, and omental reinforcement complete the closure.

From two-thirds to three-quarters of the stomach should be removed. The left gastric artery is ligated near its origin and the stomach divided between two crushing Payr clamps, the proximal clamp having a wing-nut on its tip to prevent slipping. The Hofmeister-Finsterer type of anastomosis is preferred, which brings the jejunum through a rent as far posteriorly as possible in the transverse mesocolon. The part of the cut end of the stomach other than the anastomotic site is closed by a double layer of continuous stitches, and an additional row of interrupted Lembert sutures. Precautions to be taken are the use of guy sutures to avoid kinking or rotation of the jejunum, the insertion of the posterior continuous suture well toward the mesenteric border of the jejunum so that sufficient jejunal wall is left for the remainder of the sutures, and the accurate closure of the rent in the mesocolon around the stomach or the two arms of the jejunum, as the case may be. Important structures of which damage should be avoided are the common bile duct and the middle colic artery. Drainage is used only in cases of injury to the pancreas or when there is uneasiness about the integrity of the duodenal closure.

Important points in postoperative care are continuous gastric suction for four days with only sips of water or ice allowed by mouth and a subsequent conservative attitude with regard to increasing the diet. Alkaline powders and amphogel are given regularly postoperatively. RICHARD WARREN, M.D.

McKittrick, L. S., and Sarris, S. P.: Acute Mechanical Obstruction of the Small Bowel. *New England J. Med.*, 1940, 222: 611.

This is the fourth report and analysis of the cases of obstruction of the small bowel occurring in the surgical service of the Massachusetts General Hospital. It affords an unusual opportunity for comparison of the results of treatment over a period of forty years. Strangulation obstruction has been recognized as the greatest factor in the mortality of these cases. Early diagnosis and early operation have thoroughly been instilled in the minds of every staff member of the hospital. The hazards of certain cases of late obstruction are well known and the gangrenous bowel obstruction is best treated by simple drainage of the distended loop without exploration.

There were 136 patients in the group with acute mechanical obstruction of the small bowel. From 70 to 80 per cent of all these patients had a previous laparotomy. Six per cent had been operated on for a

previous obstruction. Pain was the most common symptom present in 98 per cent of all the patients. The onset of this pain was sudden and colicky. Vomiting was present in 93 per cent of the cases. The so-called fecal vomiting was a late symptom. There was cessation of bowel movement and passage of gas following the onset of pain. The temperature was normal or even subnormal unless gangrene and perforation had resulted.

The so-called "scout" roentgen film of the abdomen is the most important single objective finding in the patient with obstruction of the small bowel. Its value from a diagnostic standpoint cannot be overemphasized. Two views are taken, one with the patient supine and the second with the patient in the sitting position. The former is superior for the gas pattern of the small bowel; the latter is superior for the determination of fluid levels. The characteristic step-ladder arrangement occurs only in the later stages.

It should be stated that there are times when the roentgen findings are most confusing.

The diagnostic criteria in acute mechanical obstruction are a history of sudden and usually severe abdominal pain, colicky in nature, in a patient with previous laparotomy; vomiting, usually following the onset of the pain; evidence of one or more distended loops of small bowel, as revealed by a "scout" roentgen film of the abdomen; and active, high-pitched peristalsis which is audible over the abdomen.

Acute obstruction of the small bowel usually occurs at a single point and is caused by a band or adhesions from a previous operation. Eighty-one per cent of the 136 cases had a single-point obstruction and simple release of this was sufficient to bring about rapid recovery. A single-point obstruction more completely predisposes to the development of gangrene of a segment of bowel than obstruction which is more adhesive and in which longer segments of bowel are involved.

There were 136 cases fulfilling all the requirements of acute obstruction of the small bowel. Eight patients were not operated on because of spontaneous recovery. Twenty-seven patients died, and 4 were not operated on in this group. The hospital mortality was 20 per cent. Of the group of 124 patients operated on, 23 died, giving a surgical mortality of 18 per cent.

In addition to a careful history and physical examination, the routine use of the "scout" film of the abdomen should make possible a definite diagnosis of early obstruction of the small bowel in a high percentage of all cases.

Strangulation is the most important single factor in determining the outcome of a case of acute obstruction of the small bowel. It was present in 33 per cent of the total group and was the cause of death in more than half of the fatal cases. Certain factors other than strangulation contribute to the high mortality, chiefly age and duration of the obstruction. The mechanical factor of bowel distention may be an important matter. The most important essential for successful operation is that the patient present himself for treatment within the first twenty-four hours of the onset. After twenty-four hours have elapsed, other factors such as distention, dehydration, and chemical imbalance rapidly assume importance. The degree of dehydration and chemical imbalance should be evaluated and appropriate methods of relief instituted. Blood transfusions are essential for certain patients with strangulation obstruction. Simple drainage of the strangulated loop of distended bowel without exploration or resection will further lower the operative mortality in most instances.

JOHN W. NUZUM, M.D.

Harrison, H.: The Importance of Simple Ulcer of the Right Side of the Colon in Diagnosis of Abdominal Disease. *Arch. Surg.*, 1940, 40: 959.

The writer presents a study of 6 instances of simple ulcer of the cecum and ascending colon. The difficulties of clinical diagnosis, the serious nature of the complications of the condition, and the unknown etiology and pathogenesis indicate that this type of intestinal ulceration deserves more study and investigation. Perforation of the bowel occurred as a result of the inflammatory process in 4 of the patients. It is apparent from the study of barium enema plates that the correct diagnosis cannot be made by means of this study alone although it may contribute valuable evidence.

The complications arising from simple ulcer of the colon give rise to a very high mortality. Perforation of such lesions may simulate perforation of an acutely inflamed appendix or may exhibit and mimic appendical abscess. Differentiation from perforated duodenal or gastric ulcer may be difficult.

JOHN W. NUZUM, M.D.

Szacsvay, I.: The Results of Treatment of Perforated Appendicitis Based on Ten Years' Material (Erfolge in der Therapie der durchgebrochenen Wurmfortsatzentzuendungen auf Grund des 10jaehrigen Materials). *Arb. chir. Klin. Univ.*, 1939, p. 205.

Appendectomy for acute and chronic inflammation of the appendix was performed 1,552 times. The mortality rate was 0.25 per cent. In the treatment of perforated appendicitis quite different results were obtained. All cases of the latter type were divided into the following two groups: (1) cases in which the entire peritoneal cavity was involved or became involved during the operation, and (2) cases of localized peritonitis. The severity of the disease and, in turn, its prognosis depend not only on the extent of its spread and on its duration, but—and this is probably of the greatest importance—on the nature and virulence of the infecting organism, and on the capacity for resistance of the peritoneum and of the body as a whole. There were numerous patients with an extremely severe process of from three to five days' duration who quickly re-

covered following operation. On the other hand, some patients who were operated upon one or two hours after perforation, who received particular care, and in whom the abdominal cavity contained only a very moderate amount of serosal exudate, died. Ljunggren, from a statistical study of nearly entire districts, established the fact that the mortality from perforated appendicitis during the last ten years was worse than that of the preceding ten years. He concluded that appendicitis had become more virulent in spite of the continuous improvement in recent years of technique, antiseptic methods of treatment, and serum therapy. The statistics of the Clinic yielded a mortality rate of 6 per cent in a single year and of 37 per cent in another similar year. This indicated a certain increased virulence of appendicitis.

There are many differences of opinion regarding the treatment of this disease. The questions arise whether or not to irrigate the abdominal cavity, and whether or not to drain it. Many and varied opinions in regard to the value of serum therapy are also heard. At the Clinic all cases are operated upon as soon as the diagnosis of appendicitis is established. The appendix is removed if at all possible. If its removal means the breaking down of localizing barriers and by this a dissemination of the infection, the appendix is left in place and the abscess cavity is drained. With diffuse processes the abdominal cavity is not irrigated. The inflammatory exudate in the abdominal cavity and especially that in the pouch of Douglas is sponged out dry. The adjacent intestines are separated by spatulas protected with tampons, which permits access to the deeper parts. Drains are always placed in the pouch of Douglas. For this purpose gauze strips enveloped in rubber drainage tubes, or large caliber glass rods with perforations in the side through the lumina of which gauze strips are drawn are used. Eleven patients were treated with "Coliperinserum" given intra-abdominally or intramuscularly. Of these 7 died. Of 282 abscesses with 25 deaths, 4 were under the diaphragm with 2 deaths. Suppurative pleurisy developed in 3 and pneumonia in 4 of the 25 fatal cases. Post-mortem examination revealed peritonitis in 16 of the cases. Of 195 patients with diffuse peritonitis who were operated upon, 64 died. Eighty-two per cent of those with perforation of the appendix who were operated upon came from the surrounding villages. Extraordinarily neglected cases were among these.

From these observations, it must be concluded that appendicitis in general is from time to time more virulent and consequently the results of treatment are poorer. These facts must be kept in mind when one is confronted with making a decision regarding the type of operation and the method of treatment. Moreover, it is certain that, to be of value, information in regard to the treatment of appendicitis should be based only on results which are collected over long periods of time.

(E. Illés). Edward W. Gibbs, M.D.

Sommer, G.: Testicular Atrophy Following Extirpation of the Rectum (Hodenatrophie nach Mastdarmausrottung). *Beitr. z. klin. Chir.*, 1939, 170: 457.

Little has been published concerning the disturbances of testicular function following extirpation of the rectum (Bauer, Dick, Goepel, Goetze). In 19 personal cases of the author, consisting only of younger patients in whom amputation and resection of the rectum or abdominosacral extirpation had been done, such disturbances occurred 6 times. Four patients complained of severe diminution of libido and potency; the volume of ejaculations was less, and the testicles had become smaller and softer. In 2 of the patients, on the other hand, there was to be noted transitory increase of the sexual vitality with a subsequent decrease. In a biopsy study of the testicle of a forty-eight-year-old man, there were to be seen considerable degenerative changes in the epithelial cells; the basal membrane was more strongly developed, the connective tissue was more abundant and appeared edematous, and the interstitial cells of Leydig were absent. The cause for these changes may lie in the inadvertent ligation of the blood vessels (the testicular arteries arising from the arteria spermatica interna and the arteria deferentialis arising from the arteria vesicalis). This, however, does not appear to be certain to the author, since a deep communication exists between the two vessels, about 2 finger breadths above the pole of the epididymis. It is also unbelievable that the vas deferens should be severed so frequently. It is much more likely that an injury of the autonomic system may be the underlying cause. The lower portion of the autonomic cord runs near the midline and extends as far as the coccyx. An injury of this portion of the cord leads to temperature elevation and through this to testicular atrophy.

Harry A. Salzmann, M.D.

LIVER, GALL BLADDER, PANCREAS, AND SPLEEN

Sandrini, G.: Congenital Anomalies of the Biliary Tract (Anomalie congenite delle vie biliari). *Clin. chir.*, 1940, 16: 227.

The author states that anomalies of the biliary tract occur with sufficient frequency to be of clinical significance. He emphasizes the surgical importance of knowledge of these anomalies. He reports a case of a twenty-two-year-old soldier, wounded during the Spanish war in the right hypogastric and lumbar regions. Laparotomy revealed an injury of the liver and the kidney and a hematoma of the gall bladder. Of particular interest was an anomaly of the biliary tract. The right hepatic duct was found to enter the cystic duct at the neck of the gall bladder and the left hepatic duct joined the cystic duct a little lower to form the common bile duct. Because of the fact that it was necessary to move the patient to another hospital, the author found it impossible to follow his course.

A presentation of the various types of congenital anomalies of the biliary tract is made on the basis of a review of the literature. These anomalies are illustrated. The author states that Schnachner classified anomalies of the gall bladder according to location and gross appearance. Several observers have reported complete absence of the gall bladder, and Phillips described a very small gall bladder which resembled the appendix in appearance.

The most common congenital anomaly of the biliary tract is the lateral implantation of the cystic duct in the neck of the gall bladder so that a diverticulum is formed at the lower end of the ampulla. Other relatively frequent anomalies are cases in which the cystic duct joins the hepatic duct at an acute angle after running parallel with it, and cases in which the cystic duct assumes an anterior or posterior spiral course to the hepatic duct entering the latter either laterally, medially, or posteriorly.

An unusual anomaly was described by Starlinger, who observed a case in which there was a bifurcation of the cystic duct and a congenital obliteration of the hepatic duct. Other anomalies have been described consisting of accessory hepatic ducts entering directly into the gall bladder or into the cystic duct.

The author quotes Kehr, who has described three types of anomalies of the biliary duct: (1) the type in which the right and left branches of the hepatic duct are united into the normal bile duct but in which two accessory ducts join the gall bladder; (2) the type in which the right hepatic duct enters the gall bladder as two branches and the left hepatic duct enters the normal common bile duct; and (3) the type in which the right and left hepatic ducts enter directly into the gall bladder and the cystic duct continues as the common bile duct. A relatively rare anomaly consists of double duodenal openings of the common duct.

The author states that Darogi described a case in which there was the unusual anomaly of the right hepatic duct entering directly into the duodenum. Delaunoy and Demarez described a case in which the cystic duct joined the common bile duct about 1 cm. from the ampulla of Vater. Leotta described an anomaly which is characterized by the hepatic ducts flowing into the neck of the gall bladder and the cystic duct being continued as the common bile duct. Reference is made to other unusual anomalies that have been described. MICHAEL DEBAKEY, M.D.

Soupault, M. R.: Therapeutic Results in Anastomoses Between the Biliary and Intestinal Tracts (Les résultats thérapeutiques des anastomoses bilio-digestives). *J. de chir.*, 1940, 55: 289.

Anastomoses between the biliary and intestinal tracts overcome biliary obstruction without external loss of bile.

In the case of malignant tumors of the pancreas, papilla of Vater, or bile ducts, the average life expectancy is from six to nine months, and the operative mortality from 40 to 50 per cent. In spite of this, these anastomoses are justifiable because of the relief from suffering afforded and because of the chance of a wrong diagnosis.

Congenital dilatation of the bile ducts is rare, causes unremitting obstruction, and occurs in young, good-risk patients. The authors prefer the choledochoduodenostomy in these cases. The results are uniformly good in spite of the fact that much reflux of intestinal contents through the stoma must occur. In two-thirds of the cases the bile duct remains patent, but this does not detract from the efficacy of the operation.

Traumatic (operative) lesions of the bile passages are of various types. Gall-bladder fistulas, when due to obstruction of the cystic duct, are cured by cholecystectomy, and when due to obstruction of the common duct, by cholecystenterostomy. Fistulas of the common duct are cured by choledochenterostomy in 52 per cent of the cases. Most successful results are obtained when the fistula has been functioning well pre-operatively. The complication most to be feared is not ascending infection but scar contracture of the stoma.

Cholelithiasis, cholangitis, and biliary dyssynergia are treated as one group. When the common and hepatic ducts are principally affected a biliary-intestinal anastomosis, and not prolonged external drainage, is indicated. Primary side-to-side choledochoduodenostomy is indicated in all cases of lithiasis of the common duct with cholangitis or when it is believed that the obstruction has not been entirely relieved by the operation. The mortality is 10 per cent and good results are to be expected in 80 per cent. In spite of the realization that the intestinal reflux often pockets in the lower end of the common duct and that the operation represents an irretraceable step, the authors consider that primary choledochoduodenostomy should occupy a prominent place beside external drainage. Secondary choledochoduodenostomy is used after failure of previous surgery of the common duct. It should not be used until after complete investigation and attempts at cure by medical means (cholangiography, attempts at dissolving stones, cholagogues, and duodenal drainage) have been carried out. Good functional results occur in 55.5 per cent, poor results in 25 per cent.

When chronic pancreatitis causes biliary obstruction it may be treated by internal drainage by biliary-intestinal anastomoses. Cholecystenterostomy for this condition produced cures in 60 per cent of the cases and external drainage in 80 per cent, but biliary-intestinal anastomoses secondary to external drainage for chronic pancreatitis produced cures in 100 per cent. In cases of hepatitis external biliary drainage is sometimes indicated, and cholecystogastrostomy may be used in cases of gall-bladder stasis. Biliary-intestinal anastomoses are never indicated in cases of gastric ulcer, although this has been advocated by some authors.

The author wishes to emphasize that anastomosis between the biliary and intestinal tracts should have a wider application. RICHARD WARREN, M.D.

Soupault, R., and Mallet-Guy, P.: The Technique of Choledochoduodenostomy (Technique de la cholédoco-duodénostomie). *J. de chir.*, 1940, 55: 313.

Soupault and Mallet-Guy note that the indications for choledochoduodenostomy may be absolute or relative. Relative indications occur more frequently and are present under more favorable conditions than absolute indications. When in cases of obstruction of the common duct the surgeon has a choice between external drainage and choledochoduodenostomy, the latter operation should be done only when the common duct is dilated and its walls are sufficiently thick for the placing of sutures in two or three planes, and when the duodenum can be well mobilized. Under such circumstances and if the incision is sufficiently large, the operation can be done successfully even in very obese patients.

The pre-operative care of the patient is important. These patients are often jaundiced, dehydrated, and anemic; and there is hepatic insufficiency often associated with renal insufficiency. In addition to the usual pre-operative measures, isotonic glucose solution should be given intravenously and the excess blood sugar balanced by insulin; the blood should be carefully examined, especially with regard to bleeding and coagulation time, retraction of the clot, and the blood count. Small blood transfusions should be given, and calcium, preferably calcium gluconate, should be administered by intravenous or intramuscular injection.

In operating on patients with obstruction of the common duct, regional anesthesia should be employed; both inhalation anesthesia and high spinal anesthesia involve definite risks to the patient. Regional anesthesia includes gradual infiltration of the abdominal wall and infiltration of the splanchnic nerve in the celiac region. For splanchnic infiltration a sufficient amount of the anesthetic, from 60 to 70 c.cm., must be used, usually in a 1/200 solution. In combination with the amount of anesthetic used for infiltration of the abdominal wall, the total amount of novocaine should not exceed 1 gm. For pre-operative sedation, barbiturates and scopolamine should be avoided; morphine should be given in divided doses during the two hours before operation. With some patients much less anesthetic is needed; this is true particularly of jaundiced patients with hepatic insufficiency.

A long vertical incision in the median line gives the best exposure for choledochoduodenostomy. After the field is well exposed, a thorough exploration of the biliary tract must be made before the operation is done.

Various techniques are employed for the anastomosis of the common duct with the duodenum. In Finsterer's technique the incision of the common duct is made parallel to its axis from the point of entrance of the cystic duct to the duodenum; this incision is made a little to the right of the median line. The incision in the duodenum begins at the termination of the choledochus and is carried toward the right along the upper border of the duodenum. A side-to-side anastomosis is made in two planes, the sutures being covered by omentum.

In the operation of Jurasz, the anastomosis is made behind the duodenum on its posterior surface. This technique brings the anastomosis closer to the papilla, and the excluded segment of the common duct is reduced to a minimum, but it requires a more extensive exposure of the duodenum.

The technique of Floercken is very similar to the preceding technique, but the exposure of the duodenum is not so extensive and the duodenal incision is transverse, although the incision of the common duct is vertical.

Whatever technique is used, a curved needle is used for placing the sutures, and non-resorbable suture material (such as silk) is preferable. Interrupted sutures are employed.

Postoperative care includes drop-by-drop infusion of glucose solution with the injection of 10 units of insulin per liter, in divided doses; calcium in large doses and blood transfusion are indicated if there is any tendency toward hemorrhage. As a rule patients rally very quickly from the operation under this treatment, and recovery may be complete in three weeks.

The authors report 12 cases of obstruction of the biliary tract in which choledochoduodenostomy was done; there was only 1 postoperative death due to renal failure and uremia. One patient died two years after operation of progressive cachexia (obstruction apparently due to cancer of the pancreas); the other patients are living and are for the most part entirely free from biliary symptoms.

ALICE M. MEYERS.

Roth, P. P.: The External Choledochoduodenostomy; Its Immediate and Late Results in Cases in which the Indication is only Relative (Die Choledocho-Duodenostomia externa, ihre Nah- und Fernergebnisse bei relativer Indikation). Frankfort on the Main: Dissertation, 1939.

The opinions concerning the operative procedure in calculous diseases of the choledochus and hepatic ducts, in stenosis of the biliary passages resulting either from trauma or inflammation, and cholangitis are still at great variance. The old method, as employed by Kehr, of drainage by means of the T-tube, is today the least used, because the continuous loss of bile leads to digestive disturbances due to insufficient fat resorption, to increased bone fragility, and to cholemic hemorrhages. This method is only exceptionally considered of value in cases with an extremely fragile choledochus, in cases in which the choledochus is deeply situated in obese patients, and in cases of ascaris infestation of the biliary passages. The dilatation of the sphincter of Oddi, as recommended by Hofmeister, has also been abandoned. The absolute indication for choledochoduodenostomy is a closure of the papilla of Vater resulting from inflammatory or actual tumors; the relative indication applies to all other diseases, especially since the

absolute freedom from danger of this procedure has been demonstrated by the experiments of Alessandri. In the latter category belong calculous conditions; scar-like stenosing processes in the biliary passages, especially those following previous operations; suppurative cholangitis with the accumulation of concrements; and idiopathic cysts of the choledochus.

We must differentiate between choledochoduodenostomy externa and interna. In the latter the choledochus is exposed through the duodenum. However, in this procedure, because of the manifold manner of the anatomical insertion of the choledochus, there is danger of injury to the pancreas. This procedure is technically difficult and has the high mortality of 19 per cent. Sasse has systematically developed the external choledochoduodenostomy. He still used the retroduodenal portion of the choledochus; to-day the supraduodenal method is employed as the method of choice.

The technique of the Floerken clinic follows:

The gall bladder is removed, and the choledochus is probed by passing a sound through the stump of the cystic duct. An incision about 1 or 2 cm. in length is made into the common duct between two guy sutures so that the duct can be employed for the subsequent anastomosis. The incision is made in a longitudinal direction, above the opening of the common duct into the duodenum. The bile which gushes out is suctioned off by means of a water pump. The patency of the choledochus is determined either by the passage of a sound, or by means of the Payr-injection method with normal salt solution. Stones are removed with the gall-stone forceps. Mobilization of the duodenum is not necessary. On the upper margin of the duodenum, in its longitudinal direction, an incision is made perpendicular to the choledochostomy incision. This is followed by suturing of the serosa with silk, and suturing of the other layers with catgut. A bit of omentum and the serosa of the hepatoduodenal ligament serve for the purpose of covering the line of suture. The wound is always packed and drainage is instituted.

Among the 113 cases a temporary flow of bile occurred, in 21 instances because the anastomosis did not hold firmly, a proof of how necessary drainage is in these cases. A permanent fistula never occurred.

The author then combats the arguments which have been made against choledochoduodenostomy:

1. The retrograde filling of the extrahepatic and intrahepatic biliary passages with barium indicates the danger of a retrograde passage of food with subsequent cholangitis. This roentgenological filling does not occur while the patient is in a standing position, but only when the patient is placed on his right side and in the Trendelenburg position. However, the specific weight of the duodenal content is equal to that of the bile, and at any rate is lighter than the barium mixture. Furthermore, it has been shown that it is particularly a wide anastomosis which protects against cholangitis much more readily than a narrow one.

2. The second argument is that a retroduodenal sac develops, in which fruit seeds and fruit skins may build ideal crystallization foci. It is for this reason that in this clinic the incision is always placed 1 or 2 cm. above the opening into the duodenum and in this manner only the smallest possible blind sac may be formed. As an exception to the rule, the author, however, does present a case in which the duodenal content found its way into the extrahepatic and intrahepatic biliary passages. In this case tomato skins became encrusted and the condition had led to the formation of a large retroperitoneal abscess in the right psoas muscle; this abscess had recently broken through into the inferior portion of the duodenum. Since then the patient has remained completely well for a period of fifteen years and has never during this time had any complaints or jaundice.

3. The third argument is that the anastomosis may become obliterated, as is evidenced by certain cases of Sasse and Finsterer. The anastomosis, however, can be obliterated only if the sphincter of Oddi again becomes capable of functioning and the papilla again becomes patent. Undoubtedly many recurrent complaints may be attributed to this complication. The wider the anastomosis, the more does one protect against the occurrence of obliteration.

All of these arguments, however, can be minimized by the usual good results. In the first place this operation is recommended because of the light operative mortality. In a statistical study Floerken determined this to be 10 per cent. In his clinic only 6 (5.3 per cent) of 116 patients died immediately following the operation. In all of these cases, he was dealing with extremely weakened patients (2 died of circulatory failure, 2 of bile peritonitis, 1 because of insufficiency of the suture line, and 1 following cholemic secondary hemorrhage). Otherwise the immediate results were extremely satisfactory. Jaundice disappeared after only a few days. The attacks of colic ceased and the patients were able to eat a mixed diet. In many instances, however, it was noted that at first mild attacks of colic and slight jaundice still occurred, no doubt because the anastomosis assumes its function only in a gradual manner.

Seventy-five patients were studied in a follow-up examination, but only those upon whom the operation had been performed at least two years previously were considered. Among these were 27 who had been operated upon more than fifteen years previously, 18 more than ten years previously, 16 more than five years previously, and 7 who had been operated upon more than two years previously. Seventy of the patients had never had any complaints at all following operation. Only 5 patients had to keep to a special diet; 4 had incisional hernias which were well retained by belts. On the average, the patient's stay in the hospital was about twenty-five days, so short a period, as compared to the length of hospitalization necessary when the hepatic ducts are drained, that it also must be taken into consideration.

HARRY A. SALZMANN, M.D.

Warren, R., and Balch, F. G., Jr.: Carcinoma of the Gall Bladder. *Surgery*, 1940, 7: 657.

Although carcinoma of the gall bladder may occasionally develop in the absence of gall stones, the great majority of cases are associated with gall stones which precede the development of the tumor. It is impossible to determine accurately the exact percentage of cases of gall stones that develop carcinoma of the gall bladder, but it probably lies between 1 and 2.5 per cent. No clinical criteria have been established to tell which cases of gall stones will develop carcinoma of the gall bladder.

Although carcinoma of the gall bladder is practically incurable once the diagnosis is established clinically, the risk of carcinoma developing in any case of gall stones is so small as not to indicate prophylactic cholecystectomy for that reason alone. The decision as to the advisability of cholecystectomy in cases of gall stones with few or no symptoms should be governed by a consideration of the danger of non-malignant complications rather than by the risk of carcinoma of the gall bladder. JOSEPH K. NARAT, M.D.

MISCELLANEOUS

Matthaes, G.: The Treatment of General Bacterial Peritonitis. A Study (Die Behandlung der allgemeinen, freien, bakteriellen Bauchfellentzuendung. Eine Studie). *Ergebn. d. Chir.*, 1939, 32: 261.

After a general review of the German literature on the subject of general bacterial peritonitis, the author goes into the anatomy of the abdominal cavity, the physiology of the peritoneum (resorption, exudation, plasticity), and the nature of bacterial peritonitis. Matthaes states that the fundamental aim in the operative handling of peritonitis is the elimination of the infection as completely as possible. The necessity for rapid and atraumatic surgery is also emphasized. In perforated peptic ulcer the opening should be closed and gastro-enterostomy or resection deferred. The gall bladder is removed only in early cases, and in others drainage is instituted. Early operation in peritonitis is generally approved, apparently because of the more favorable end-results. In contrast to this it must be noted that the late operative mortality is very high. Matthaes tends to follow a routine of handling all cases of peritonitis seen within forty-eight hours regardless of the condition, age, or constitution of the patient, and does not advocate individualization of the cases. In peritonitis originating by means of the lymphogenous or hematogenous routes, such as pneumococcus and streptococcus peritonitis, surgical elimination of the infection is impossible. Pneumococcus peritonitis is primarily a disease of children and because of the richness of the fibrinous exudate there is a tendency toward encapsulation. Therefore, expectant treatment seems proper in these cases. The prognosis depends upon the severity of the infection and the resistance of the peritoneum rather than upon any type of incomplete operation. Encapsulated abscesses should be drained. On the other hand, streptococcus peritonitis shows little tendency to become walled off. The usual virulence of this organism makes the prognosis much more unfavorable. Infections entering through the female genital organs, especially gonococcal, are generally benign and healing occurs without the aid of surgical measures. Matthaes states that the intraperitoneal instillation of Behring's "peritoneal serum" through a small catheter after primary closure of the abdomen is a prophylactic measure of some value. It may be used in cases such as those subjected to colon resection for tumor, in which some degree of peritonitis is anticipated. The serum is not indicated in aseptic operations because it has not been shown that the serum will protect the peritoneum against infection in every case. Matthaes finds no marked difference between the mortality rates when the exudate has been removed by sponging or by irrigation. Both methods have their advantages and disadvantages. Early removal of exudate should be avoided. When marked soiling is present, as in perforated peptic ulcer, irrigation is preferred. Irrigation works mechanically. Whereas in cases with a rich exudate and a great deal of pus, as in generalized peritonitis, it is better to avoid irrigation; in fibrinopurulent forms irrigation is a mistake. Circumscribed peritonitis is sponged out.

As regards anti-bacterial therapy, the author differentiates the chemical and biological antiseptics from those agents which inhibit resorption and those that stimulate the formation of exudate. Matthaes does not find the chemical substances such as rivanol, alcohol, colloidol silver, and ether of much value. It is impossible to disinfect the abdominal cavity. The situation is somewhat different with biological antisepsis. Substances which the body uses to protect against infections, such as n/20 hydrochloric acid, or hydrochloric acid pepsin are employed. With or without the presence of pepsin the acid is quickly neutralized in the abdomen; therefore the action on bacteria must be very short. The oil method, with camphor oil, has been discarded. Absorption of toxic substances by the peritoneum is the threatened danger; this occurs by way of the blood system. Irrigation with hypertonic solutions such as 50 to 80 per cent sugar solution or 10 per cent sodium chloride is possible only if a continuous flow of secretions to the outside is present. The peritoneal cavity can be drained for only a short time, and, in addition, this type of treatment upsets the water balance of the entire body.

The author differentiates between tamponade and drainage. The gauze placed in the wound rapidly absorbs everything to its fullest extent because of capillary attraction and thereafter acts as a plug. This results in stagnation of the exudate which may lead to marked bacterial proliferation. Tamponade works satisfactorily because of the adherence to structures when extensive infection is present and aids in packing away edematous necrotic parts. Drainage in the free peritoneal cavity is indicated

only in late cases. When the exudate is rich and there is marked agglutination of the loops of bowel, drainage is possible for only a short time. The Rehn-Fowler position does not seem to influence the end-results. So-called local drainage is to be differentiated from drainage of the free peritoneal cavity. Primary closure of the abdomen in peritonitis due to appendicitis seems to be a good principle, but its generalization must not be too great. Matthaes is of the opinion that primary and secondary types of infection are eliminated by the peritoneum. Various types of serum (Behring's peritonitis serum, colon and perfringens antitoxin) may be used intraperitoneally, intravenously, or intramuscularly with good results. It has not been definitely proved that these results are due to the disappearance of the peritonitis. One must bear in mind the danger of anaphylaxis.

In closing, Matthaes discusses briefly the postoperative treatment as regards circulation, peristalsis, vomiting, hiccoughs, and thirst. He stresses the importance of prophylaxis against peritonitis. Early recognition of peritonitis is essential. One must appreciate the two opposing factors of infection and individual resistance. All possible means must be taken not to disturb or destroy the natural biological resistance for the outcome depends largely on the ability of the individual to wall off the infection. (GEBELE). JOHN A. GIUS, M.D.

Lehman, E. P., and Boys, F.: The Prevention of Peritoneal Adhesions with Heparin. An Experimental Study. *Ann. Surg.*, 1940, 111: 427.

(To replace previous abstract on pp. 39 and 40 of this volume.)

In two sets of experiments with corresponding controls, heparin was found by the authors to be astonishingly effective in preventing adhesions when introduced into the peritoneal cavity of the dog and rabbit. The number of experiments is limited and the work has not progressed sufficiently to warrant application to the patient. If the experimental value of heparin in preventing adhesions is confirmed by other investigators, its use will offer considerable promise for this heretofore essentially unsolved problem.

The permanent fibrotic peritoneal adhesion is the final result of organization of a fibrinous inflammatory exudate between two apposed injured peritoneal surfaces. At first the exudate is serous or seropurulent and unclotted, but it soon becomes coagulated and a fibrinous adhesion is formed. Once the apposing mesothelial layers are destroyed in this zone, the exposed subperitoneal connective-tissue and blood-vessel elements are stimulated to proliferate over the fibrin scaffolding. The organizing process eventually replaces the fibrinous adhesion and a permanent fibrotic adhesion remains. Since heparin has been found by other investigators to prevent thrombosis, it seemed logical to the authors to believe that heparin might also be used effectively in preventing the coagulation of the inflammatory peritoneal exudate, and thus preclude adhesion formation. The heparin anti-adhesion attack is concerned with preventing fibrin formation and not with its removal once formed. These preliminary animal experiments were conducted to test this hypothesis.

In 56 rabbit experiments, adhesions were produced by two methods, mechanical damage and bacterial contamination to the peritoneum. The mechanical peritoneal injury was effected by a modification of Donaldson's pledget technique, while the peritoneal contamination was produced by perforating the appendix and expressing a small measured quantity on adjacent serosal surfaces. In the latter method the appendix was always emptied and the perforation was not closed. When these two types of peritoneal damage had been surgically produced, a control group (no solution, normal saline and amniotic fluid) and an experimental group (heparin) were established. Equal amounts of the respective solutions were then introduced intra-abdominally before closure at this operation. These injections were repeated by paracentesis on the ensuing two postoperative days. The results indicate a striking difference in the number of formed adhesions between the control and experimental groups. In the mechanical-trauma experiments (36 animals), all of the different 26 control animals showed adhesion formation, but only 1 of 10 of the heparin-tested animals presented any adhesions. In the contamination experiments (20 animals), the results were similar. All of the 10 controls showed adhesion formation while none of the heparin-treated animals produced adhesions.

In 40 dog experiments, designed to re-create the frequent surgical problem presented by adhesions needing division on account of intestinal obstruction, the results suggest that heparin is quite effective in preventing adhesion re-formation. Adhesions caused by peritoneal contamination were produced exactly as in the rabbit experiments, but approximately half of the dogs died from peritonitis following this procedure. Six weeks later, at a second laparotomy, the formed adhesions were counted and divided. At the same time control and experimental groups were established as in the rabbit experiments described, and equal amounts of the respective solutions were introduced into the peritoneal cavity before closure. These injections were also repeated by paracentesis on the first and second postoperative days. Two weeks later the re-formation of adhesions was observed at a final laparotomy. In all of the control groups a greater number of adhesions reformed than were divided. The average number of formed adhesions in the combined control groups before division was 8, while the average number of re-formed adhesions was 12.6. This makes a reformation rate of 157 per cent for the control animals as a group. In contrast, the heparin-treated animals presented only about one-quarter as many re-formed adhesions. The average number of formed adhesions in the experimental group before division

was 9.7, while the average number of re-formed adhesions was 2.6. The re-formation rate here, then, is 26 per cent. This numerical difference is less striking than the difference observed at celiotomy, in which it was seen that the adhesions following the introduction of heparin were uniformly single strands, whereas those in the controls were usually broad bands and sheets.

The chief danger in the employment of heparin seems to lie in the occurrence of hemorrhage. Three dogs of the 24 receiving heparin suffered massive intraperitoneal hemorrhages, all fatal. Heparin prevents the formation of fibrin but does not dissolve or destroy it. It is logical, therefore, to assume that hemorrhage should not be a danger in the intraperitoneal use of heparin provided complete hemostasis is assured before closure of the abdomen. It is assumed that in the 3 hemorrhages here reported, all of which occurred early in the study, this essential was not observed. A wider animal experience is believed necessary before the method can be condemned for this reason.

If heparin is found useful against the formation of adhesions in the peritoneal cavity, it is conceivable that it may also be employed effectively in other serous cavities, such as the pleural cavity, the pericardial sac, the subarachnoid space, and the various joints.

GYNECOLOGY

UTERUS

Savignoni, F.: Hysterosalpingography in Sterility (L'isterosalpingografia nella sterilità). *Clin. ostet.*, 1940, 42: 101.

The first attempts at hysterosalpingography were made in 1914 when Cary injected collargol and Kennedy used 40 per cent sodium bromide. The author briefly sketches the Italian contributions in this field since then. He describes the manometers and methods of injection used with suitable pictorial illustrations. By such means motor activity may be demonstrated in the tubes. This activity is: (a) sphincteric, (b) peristaltic and anti-peristaltic, and (c) pendular.

The author studied 100 sterile women by means of hysterosalpingography. The husband was examined for sterility in each case. In no case was the procedure carried out when there was evidence of active inflammation or cervicitis. The most favorable time to do hysterosalpingography is between the ninth and fifteenth days of the intermenstrual period.

In his description of the technique the author notes that he never exceeds a pressure of from 200 to 250 mm. of mercury in performing the injection. He finds that the failure of complete passage of the oily medium through the tubes at the first trial is no proof of tubal obstruction. He records cases in which the second attempt was successful. In real obstruction of the tubes the medium does not enter the abdominal cavity. A frequent finding in these sterile women was a tortuous course of the tubes (Fig. 1). Such a condition is an obstacle to the meeting of the spermatozoa and the ovum. A frequent finding in these women was a congenital distortion in the position of the uterus (Fig. 2).

The procedure of hysterosalpingography has had a curative effect on the sterility of some women

Fig. 1.

Fig. 2.

with mild tubal obstructions. Congenital deformities were demonstrated in some. This method is particularly suitable for demonstrating congenital anomalies and deformities in the development of the genital tract. It is also suitable in diagnosing disturbances of position and after-effects of inflammation in the genital apparatus. Numerous illustrations are presented. JACOB E. KLEIN, M.D.

Goodall, J. R.: Endometrioma Interstitiale: Preliminary Report. *J. Obst. & Gynaec. Brit. Emp.*, 1940, 47: 13.

Interstitial endometrioma is a disease in which the interstitial cells of the endometrium have taken on invasive and vicarious growth beyond the normal bounds of the endometrium. The author notes that sarcoma of the uterus is a very rare disease. Older cases, some reported herewith, first diagnosed as sarcoma, and later re-studied by the author, were found to fall into the non-malignant and curable type of interstitial endometriomas. Two distinct clinical types of the disease appear. In one there is a uniform symmetrical enlargement of the uterus, even to the size of a three months' pregnancy, due entirely to thickened walls from new growth infiltration and concomitant stimulation of associated fibrous and muscular tissues. The endometrium may be normal or greatly thickened. In the second clinical type there is a definite tumor formation of the uterus with the gross characteristics of a fibroid. This may be multiple. In the same instances, large cysts containing clear, straw-colored fluid were found within the larger nodules. In 5 of the 14 cases described by the author, an extra-uterine endometriosis was also found at operation. It is assumed that there is a common cause of the two conditions.

In this monograph, the author presents in detail studies of interstitial endometrioma as found in 8 patients. He concludes that interstitial endome-

trioma is a disease *sui generis* and that it is of very common occurrence. It may be acute, simulating a sarcoma, or may be so chronic as to resemble richly cellular fibroids. It may be diffuse, involving all the walls of the uterus, or specifically affect only one part; when diffuse and chronic, it closely simulates chronic fibrosis uteri.

The author concludes that von Recklinghausen's disease (adenomyoma) is not a congenital but an acquired disease, similar in every respect to a local interstitial endometrioma, but with the added differentiation of the occurrence of some of the endometrioma cells in associated glands. The active agent, estrin, in the production of an interstitial endometrioma, usually stimulates other structures of the secondary sex organs into growth activity, and the provocative agent is probably the unrestrained growth hormone, estrin. The removal of the ovaries, or their functional destruction with radium or the x-rays, removes the source, and since nature is constantly endeavoring to restore the normal balance, spontaneous regressions and recoveries are fairly common. The growth hormone, when in excess, is an inhibitor of pregnancy, for, although the fallopian tubes are commonly patent in endometriosis and endometriomas, pregnancy rarely supervenes.

HERBERT F. THURSTON, M.D.

ADNEXAL AND PERIUTERINE CONDITIONS

Kaeuffler, R.: Chorio-Epithelioma of the Tube. Report of a New Case (Das Chorionepitheliom der Tube. Bericht ueber einen neuen Fall). *Zentralbl. f. Gynaek.*, 1939, p. 2377.

Fifty-two cases of chorio-epithelioma of the tube have been reported in the literature. A new case is added. A forty-year-old para-vi with a history of regular menses came to the clinic reporting bleeding of two and one-half weeks' duration beginning ten days after her last period. On examination, a normal uterus was found and a thickening of the right adnexa. A tubal pregnancy did not seem probable since the usual symptoms were lacking. The patient was released after the administration of "secale" and hormone from the posterior lobe of the pituitary gland. She was told to return in a week. After about six weeks she returned with the information that after a cessation of the bleeding for four and one-half weeks, heavy bleeding had recurred. On the right side and behind the unchanged uterus a solid tumor was palpated. It was the size of a man's fist, slightly mobile, and inflammatory.

Since no improvement was obtained with conservative management, the tumor had increased to the size of a child's head, and the patient had become febrile, a laparotomy was performed. The tumor was removed together with the tube which had grown to the size of a hen's egg.

Macroscopically the tumor resembled a chorio-epithelioma in its spongy, soft consistency and gray-red color. Sixteen days after the operation the Aschheim-Zondek test was negative. A second test four days later with concentrated urine and also with urine in a dilution of 1:200 gave a positive test. On the twenty-sixth postoperative day the patient died with cardiac complications.

Autopsy showed metastases in the lung and liver besides a marked cachexia and anemia. The greater portion of the tissue removed at operation consisted of the distended tube which was filled with hemorrhagic and chorio-epitheliomatous tissue.

A detailed, critical comparison of the observed cases with the present case was made, the details of which should be read in the original.

(W. REIFFERSCHEID). RONALD R. GREENE, M.D.

EXTERNAL GENITALIA

Folsome, C. E.: Tumors of the Vulva. *J. Am. M. Ass.*, 1940, 114: 1499.

The author's experience points to the fact that a better general understanding of benign tumors of the vulva is an important part of preventive gynecology and is therefore essential in the proper insight and control of vulvar cancer. The greatest error in the management of these lesions is in the inadequate emphasis on the metaplasia and malignant change in apparently benign vulvar tumors. Papillomas, sebaceous cysts, pigmented moles, leiomyofibromas, vulvar breast tissue, and sweat-gland adenomas are some of the benign lesions which may at a later period in a woman's life degenerate into vulvar malignancy.

The characteristics of these tumors are discussed and the author then points out the malignant changes found in the cases of vulvar tumors of some standing prior to their admission to the hospital.

While sarcoma of the vulva is rare, its evolution is usually rapid. It may develop in the vulvar end of the round ligament or may be primary in the vulva. This lesion is usually irregular, modulated, and covered with a thin layer of epidermis. It may resemble a fibroma of the vulva until ulceration has taken place. In the sarcomas reported upon by the author, the inguinal glands were involved in all cases, which finding was in contrast to the findings of Frank who stated that these glands were rarely affected. In spite of the tenet of some pathologists, that fibrosarcomas tend to remain localized, the author stresses that these tumors may actually undergo wide hematogenous spread.

Metastatic malignant tumors of the vulva are rare, as are basal-cell carcinomas. They appear as small indurated and ulcerated tumescences usually found on the labia majora.

Carcinoma of the vulva is the most common malignant neoplasm of the external female genitalia. Vulvar cancer is primarily a tumor of senility, with the greatest incidence during the sixth and seventh decades. The symptoms stressed as characterizing carcinoma of the vulva were pruritus, tenderness, soreness or actual pain, and "spotting" or irritating leucorrheal discharge, and if one waits for these cardinal symptoms to appear before making the

diagnosis, there is little hope for a favorable prognosis.

The author believes that the treatment of vulvar cancer is becoming more rational in the light of present anatomicopathological knowledge of these lesions. Surgery of the vulva, combined with resection of the superficial and deep inguinal lymph glands, the so-called Basset technique with modifications by Taussig, continues to be the best treatment for carcinoma of the vulva. ANTHONY F. SAVA, M.D.

MISCELLANEOUS

Kreis, J.: The Concealed Cycle and the Functional Cycle in Women (Cycle inapparent et cycle fonctionnel chez la femme). *Rev. franç. de gynéc. et d'obst.*, 1940, 35: 3.

This article is a mathematical discussion of the menstrual cycle. The author wishes to show that although women have a perfectly obvious menstrual cycle of 28 days, there is a definite time relationship connected with every interruption of menstruation. Thus, if an amenorrhea develops, for one reason or another, the reappearance of menstruation has a definite time relationship to the last period. There is a common factor of 7 days. The usual cycle is 28 days, that is, 4 x 7. There are other cycles of 21 days, that is, 3 x 7, and lesser known cycles of 35 days, or 5 x 7. He points out that the usual period of gestation is 280 days, or 40 x 7. In certain cases of amenorrhea he has found it necessary to do a curettage and has found that the uterine mucosa was in a phase that corresponded to that to be expected if the patient had continued to menstruate.

When labor is apparently delayed beyond the expected date, it occurs generally 7, 14, 21, or 28 days later. The return of menstruation after labor has a very definite relation to the date of confinement or to the cessation of lactation. And here again the time interval is a certain number of days. As a rule the patient's usual rhythm carries through labor and lactation so that menstruation reappears on a day that could be calculated from her last period. However, there are some patients in whom the confinement would seem to set a new rhythm so that the menstrual cycle starts from this point. In many women, the return of the periods following labor occurs in 6 weeks, that is, 6 multiplied by 7. Occasionally periods return 7 weeks after confinement. The author was struck by the conspicuousness of the 7 factor.

In conclusion, it may be stated that there are certain definite factors in the re-establishment of menstruation following any interruption of it, and it will be found that this re-establishment occurs some time after the last regular period that is divisible by 7. ADRIEN VERBRUGGHEN, M.D.

Reynolds, S. R. M.: Gynecic Physiology and the Gynecologist. *Am. J. Surg.*, 1940, 48: 175.

This is a review of the number, nature, and interrelationships of the gonadotropic and sex hormones, with a consideration of their effects.

The gonadotropic hormones are those which are capable of inducing directly characteristic changes, of a stimulating nature, in the gonads of suitable experimental animals. Today, the gonadotropes are held to be: (a) of anterior pituitary origin; (b) of chorionic origin; and (c) those typical of pregnant mare's serum, the active principles of which probably arise from the placenta.

None of the gonadotropes has been isolated in purified form. Despite this fact, extracts are now commercially available, which are said to be predominantly "follicle-stimulating" or "luteinizing." Their true effects on the human ovary may not be accurately stated at the present time. Hence, their use at this time is empirical and should be recognized as such in the evaluation of successes and of failures.

The gonadotrope, prolan, or the chorionic gonadotropic hormone is associated with human pregnancy, or neoplasms arising out of pregnancy. It has not been shown to be capable, when acting alone, of inducing luteinization in monkeys or women, and in those forms in which it does induce luteinization most readily, the placenta does not elaborate appreciable or even measurable amounts of such a hormone.

The relation of equine gonadotropes to prolan and anterior pituitary gonadotropes remains to be established. Some reports have indicated that ovulation may be induced in women by equine gonadotropes, although the published results to date are equivocal.

Little may be said at this time regarding the ultimate value of gonadotropic substances in endocrine therapeusis. The most important aspect of current work lies in what is known of their presence in the blood and urine under normal and abnormal circumstances as a diagnostic aid. Their significance in the early determination of pregnancy (Aschheim-Zondek and Friedman tests), in the early establishment of ectopic pregnancy, and the detection of chorioepithelioma are cases in point.

In the absence of pregnancy, the detection of gonadotropes in the blood and urine requires special concentration (extraction) of the hormones. In normally menstruating women it appears that a gonadotropic substance may be obtained in the midcycle. More important is the fact that it is far more abundant in urine obtained during afunctional conditions (operative castration, radiation castration, postmenopause, amenorrhea of long standing) as well as in certain hyperhormonal conditions (climacteric, irregular menses, polymenorrhea). According to Fluhmann, it is seldom found in hypohormonal cases (irregular menses, scanty menses, amenorrhea of short duration).

The number of native sex hormones is now known to be few, and these lend themselves to grouping into (a) gynecogenic substances, comprising both estrogens and progestogens, and (b) androgenic substances. The structural formulas of these and other important related substances are now known.

An *estrogen* may be defined as a substance derived from natural, artificial, or synthetic sources, which

brings about in immature, ovariectomized, or senile female animals growth of the accessory sexual glands (uterus, tubes, vagina, and breasts) to normal (mature) or supernormal size. They are called estrogens because they are capable of producing changes which simulate the specific histological and functional changes characteristic of estrus in certain laboratory animals.

A *progestogen* is a substance which, acting upon a uterus first stimulated by an estrogen, causes further growth, marked glycogen deposition, secretion of the uterine glands, and hyperplasia of the glandular epithelium and of the muscular elements of the myometrium. These changes are necessary for implantation and the maintenance of gestation, whence comes the name "progestin" devised by Corner and Allen.

An *androgen* is a substance which, when injected into an immature or castrated male animal, elicits extensive growth of the seminal vesicles, spermatic cord, prostate gland, penis, and Cowper's and the preputial glands.

The important facts concerning the relative potencies of various estrogens are not so well known. The several primary estrogens are, almost without exception, *qualitatively* identical in their effects, yet striking *quantitative* differences between them have been clearly established. Such differences are clinically important because they affect not only the time of onset of a given response but also the amount of hormone and the duration of the response which a given mass of hormone will elicit. The latter is important since it governs the frequency with which the hormone must be administered.

The relative effectiveness of a number of estrogens by the uterine growth test reveals the following series in decreasing order of effectiveness per unit mass of hormone: estradiol, estradiol benzoate, estrone, equilin, equilenin, estrone benzoate, estriol. The order of this series is not basically important, however, because estriol, last in the series, is the most potent estrogen when taken by mouth.

Determination of the threshold dose of estradiol, estradiol benzoate, and estradiol dipropionate for the induction of estrus shows that estradiol is about twice as effective (by mass) as either of the 2 other substances. If, however, one considers the *duration* of the estrus induced by the same threshold mass of each hormone, the dipropionate ester is many times more effective than estradiol, while the benzoate ester is intermediate in this respect.

The foregoing considerations show clearly the futility of attempting to gauge the relative potency of several estrogens on the basis of one phase of a twofold response, threshold and duration. It is also unfortunate that many of the estrogens are not expressed in the same units, as there is great confusion when one attempts to compare dosages.

The clinician may well ask what he is to do to obtain the greatest effectiveness from a given dose, when the label on the box gives no true indication of the relative potency of its contents. The entire question of standardization should be reopened by the proper authorities, and a true basis for comparison agreed upon. In the meantime, the physician would do well to adopt some one type of estrogen in his practice, learn by experience how much and how frequently it must be given to obtain a desired effect. In general, esterification prolongs the action of an estrogen, while reducing its threshold for the induction of estrus.

In the urine of both men and women, gynecogens and androgens are found. The identity of the urinary androgens and estrogens has not been fully established.

The bisexual properties of a number of gonadal hormones have been investigated under a variety of conditions. Experiments by Korenchevsky on gonadectomized rats have established that nearly all the sexual hormones investigated tend to a greater or less degree to restore to normal both the male and female sexual organs, which have atrophied as a result of gonadectomy. Testosterone propionate brings about a return to normal, or even supernormal, of the atrophied sexual organs of castrated males. The same hormone also restores the structure of the atrophied uterus and vagina of an ovariectomized female to a condition not far from normal, while the weight of the vagina and the development of some of the tissues of this organ is even supernormal.

The relative effectiveness of the hormones, acting alone, in stimulating female sexual organs is as follows: estradiol, estrone, testosterone propionate, testosterone, androstanediol, androstenediol, androstendione, transydro-androsterone, androsterone, progesterone. Transplants of ovarian tissue into the ears of castrated male rats will sustain the accessory organs of reproduction. The bearing which such hormones have on varying grades of intersexuality is obvious.

A number of recent reports suggest that testosterone or testosterone propionate may be useful in gynecological practice. The conditions in which it has been used successfully are: cyclic mastalgia, functional uterine bleeding, essential dysmenorrhea, premenstrual tension, and the menopause syndrome; it has also been used for the relief of after-pains. It is as yet too early to state what dosages may be employed safely in any given case and yet be therapeutically effective. It appears that masculinization may be detected if dosages of from 500 to 600 mgm. of testosterone propionate are used in a given course of treatment lasting some two weeks. Consequently, androgen dosage must for the present be empirical.

It is impossible to visualize the rôle of androgens in the etiology of specific gynecological pathology, other than in cases of intersexuality. The fact that such substances are normal excretory products in the urine of women leads one to surmise, as Korenchevsky has done, that failure to consider the possible interplay of gynecogens and androgens is the basis of the failure, in the past, to interpret correctly the endocrine basis of a variety of common gynecological conditions.

Within the past few years, a number of substances have been obtained which bear no structural resemblance to the natural estrogens, i.e., no sterol nucleus, yet they are highly estrogenic. Qualitatively, some of these substances compare with the natural estrogens in potency. The best known of these is stilbestrol.

All reports agree that stilbestrol is a very potent estrogen in women; that it is highly efficient when given by mouth, being but little inactivated in the processes of absorption and utilization (as natural estrogens are, especially in the human being); that it is an effective agent in reducing the number and severity of menopausal flushes; and that it simulates natural estrogens in other important respects. There is *not* agreement, however, regarding the incidence of toxicity nor in the toxic manifestations which it elicits.

The opinions of some authorities on the possible harm from estrogen therapy should warn against long-continued and indiscriminate therapeutic use. In this connection the possibility of carcinoma induced by estrogens cannot be ignored.

The sex hormones are mistakenly regarded as having effects which are confined to the secondary sex organs. Such a view overlooks the fact that these hormones may have other actions and that these, in turn, may have desirable therapeutic effects, or possibly undesirable ones.

The chief clinical use of estrogen for its general effects is in the treatment of the vascular disturbances of the menopause. There is no question about the specific nature of the relief which it affords in the majority of cases. There is evidence that estrogens have a vasodilating action on the smallest blood vessels in certain parts of the body. The following facts suggest this: the injection of estrogen causes swelling and changes in the water content of the sex skin in certain primates; estrogen causes engorgement of the blood vessels in the nasal mucosa; the injection of estrogen in the human being is followed by a fall in the capillary pressure and dilatation of the nail-bed capillary vessels; estrogen causes a decrease of venous pressure in the hand; and, finally, estrogen causes a change in the water content of the skin of the rat within a few hours.

The mechanism by which the vasodilating action of estrogen is exerted in the skin vessels of human beings and rabbits has not been established. Facts of an indirect nature support the idea that it may be associated with an increase in the tissues in the concentration of acetylcholine.

The consequences of these vascular effects of estrogens upon the cutaneous circulation remain a matter of speculation. As these vessels are primarily concerned with heat loss from the body, the view has been advanced that at least a partial explanation of the beneficial effects which estrogen exhibits in treatment of the vascular disturbances of the menopause is to be found in increased radiation of heat from the body. This should minimize the need for the intermediation of nervous factors, which result in sweating, and periods of temporary arteriolar dilatation, as occur in the menopausal flush.

Estrogen causes uterine hyperemia. By means of the initial vasodilatation in the uterus, a ready access of estrogen to the tissues is assured. Subsequently, other, anabolic effects of the hormone are effectively exerted upon the uterus.

The true effects of sex hormones on the formed and unformed constituents of the blood are as yet not established.

The relation of total oxygen consumption to the menstrual and sexual cycle is not clearly understood, but it is established that the sex hormones have marked and characteristic effects upon the metabolism in certain specific tissues. In proestrus, estrus, and during parturition of rats, the metabolism of the liver, ovary, anterior pituitary gland, and thyroid tissues is higher than at other times. These cyclic fluctuations are abolished by spaying, and they may be simulated by the injection of estrogen. The anterior pituitary gland responds first to the hormone, second to the thyroid gland, and third to the liver. In view of the established histological relationships between the anterior pituitary gland and the ovary, on the one hand, and between the ovary and the uterus, on the other, it is probable that the heightened metabolic processes of the pituitary gland bear a causal relation to the concurrently elevated metabolism in the uterus. Because of the rôle of the liver in carbohydrate metabolism, the periodic changes in carbohydrate metabolism in the liver may well contribute to the selective burning of carbohydrates in the uterus during estrus.

Not the least of the numerous effects of the sex hormones is their influence upon the water and salt content of various tissues. Just preceding the time of menstruation one may frequently observe a generalized edema, an increase in capillary fragility, and a retention of sodium chloride. Careful studies on pregnant women have established that the water retention which occurs at this time is associated with the retention of sodium chloride. This is favored most particularly by estrogens, and involves tissues generally. Sex hormones contribute to conditions now known to govern the water and electrolyte pattern of intercellular and intracellular fluids.

The effect of estrogens on the water content of tissues has been demonstrated in the case of the uterus of the rat and monkey and certain other tissues, especially the skin and subcutaneous tissues. The first effect of estrogen is to increase the amount of water in the intercellular phase of the uterus. It shows that an increase in the amount of protoplasmic substance of the uterus is preceded by an appreciable hydration of the tissues. Along with the changes in water content of the uterus are other, equally marked, changes in the electrolyte pattern of the uterus. Present data show that in the follicular phase of the rabbit, the concentrations of sodium and calcium are at a maximum, the potassium and magnesium at a minimum. In contrast, during the luteal phase, conditions are reversed.

Concerning the relation of sex hormones to pigmentation in the skin, if hypogonadal individuals (male or female) are exposed to sunlight, they fail to tan readily although an invisible change takes place in the tissue. Thus, if androgens or estrogens are injected subsequent to exposure to ultraviolet light, pigmentation of the skin occurs without further exposure to light. The relation of this phenomenon to carotene and melanin deposition is unknown.

Regarding oxidation-reduction and sex hormones, there is little one may say at this time about the presence of specific enzyme systems of the uterus and other tissues on which the sex hormones act in order to regulate the necessary energy for various aspects of uterine functions. However, the author believes that it is in the determination of the kind and distribution of enzymes, or in the local conditions under which these systems work, that the sex hormones govern the several aspects of reproductive function.

The metabolism of gynecogens; interconversion of the estrogens. There are three primary estrogens: estrone, estradiol, and estriol.

Estriol is an end-product of estrone and estradiol conversion in the body.

Estrone is modified when injected into rabbits according to the condition of the reproductive tract. Estrone is converted into estriol in the uterus, and for this to take place the uterus must be under active ovarian control, since several months after castration, conversion does not take place. Regardless of whether estrone or estriol is excreted in the urine, the total estrogen recoverable represents only a fraction of that which is injected; consequently, destruction of estrone as well as of estriol takes place *in vivo*.

Regarding the destruction of estrogens in the body, it seems certain that the liver is primarily involved.

Estradiol is found in only minute amounts in the urine after the injection of estrone into rabbits; there is, therefore, little conversion of the ketone into the diol form. Estradiol is rapidly converted into estrone; this substance is, in turn, partially converted into estriol, provided that functional uterine tissue and progesterone are present.

Progesterone has important effects upon the metabolism of estrogens. It increases the quantity of estrogen excreted in the urine, presumably through a sparing action of the estrogens from destruction by the liver enzymes. How this is brought about is not known. Progesterone's second action is in the conversion of estrone to estriol, in which it acts in conjunction with functional uterine tissue.

The foregoing facts explain the well known increase in blood and urinary levels of estrogen in the latter (luteal) part of the menstrual cycle. It now appears that in the early interval there is a different type of estrogen metabolism involving a high degree of estrogen destruction. Estrogen production continues at a high level throughout the menstrual cycle, with increased excretion, as progesterone spares it from destruction by the liver.

Two other aspects of progesterone metabolism in the endometrium deserve mention: it gives rise to glandular growth and permits ovum growth. The effect of the several primary estrogens on each of these endometrial effects of progesterone is not identical. Estrone inhibits both egg growth and glandular proliferation, whereas estradiol and estriol do not, though they decrease the degree of glandular proliferation.

Considerations of the foregoing sort suggest that in the uterine metabolism of estrogens, a chain, or group, of reaction systems acts upon, or requires the participation of, the hormone molecules. "The vaginal effect presumably occurs at a point in the chain wherein rather wide variation in chemical structure does not necessarily hinder activity. Participation in certain of the uterine reactions on the other hand requires more specific structural configuration; the reactions involving ovum growth, for example, are unaffected by certain native hormones which do affect both uterine proliferation and vaginal activity." (Pincus and Werthessen).

The end-products of the metabolism of progesterone in the body are just beginning to be worked out. It is likely that pregnandiol (combined in the liver with glucuronic acid) is the principal urinary end-product of such metabolism in the human. This substance is present in the urine during the latter part of the menstrual cycle. It is present in human urine through pregnancy, even after ovariectomy early in pregnancy. This signifies that progesterone is produced in human pregnancy outside of the corpora lutea, most probably in the placenta. Pregnandiol may not be the sole end-product of progesterone metabolism, even in women, because some women excrete pregnandiol in the absence of a well-marked premenstrual endometrium; some women with premenstrual endometria do not excrete pregnandiol; and, finally, pregnandiol is not found in the urine of laboratory animals, even after the injection of progesterone. Since less than half of injected progesterone is recovered in the urine of women, a large share of it remains to be accounted for.

Regarding carcinogenesis and estrogens, the following is of interest. It *is* possible to produce carcinomas in mice—but only mice thus far—by injecting estrogen for long periods of time in immature female or mature male mice of strains in which most of the females develop mammary cancer between the ages of six and twelve months. Such tumors are truly carcinomatous, since bits of this tissue transplanted to untreated males grow into tumors which are lethal without further estrogen treatment. In immature females subject to prolonged estrogen treatment, cervical cancer may be produced if the mammary cancer, which invariably appears first, is repeatedly trimmed away.

To summarize, true carcinomas have been produced only in strains of mice which have a strong genetic susceptibility to carcinoma; without this genetic factor, estrogens have never been shown to be carcinogenic.

Estrogens cause uterine growth, eliciting marked hyperplasia of connective-tissue elements in the uterus, with subsequent conversion into smooth-muscle elements. Estrogen favors extensive mitosis in the epithelium of the endometrium in normal growth and repair. Progesterone, in addition to the well known progestational proliferation of the endometrial glands, causes mitotic division of the smooth-muscle elements of the myometrium; it does not, however, favor hypertrophy of these tissues.

Estrogens may influence the condition of the cervical mucus with respect to its suitability for the transmission of sperm and thus be of importance in sterility. The view that a special "bleeding hormone" of the anterior pituitary lobe is responsible for the onset of menstruation is now discredited. The immediate stimulus for menstruation in all probability resides within the uterus.

Menstruation may be induced in monkeys and in women by a variety of methods. It occurs soon after withdrawal of the hormone in a course of estrogen treatment in ovariectomized monkeys or women; it occurs after ovariectomy during a functional cycle; it takes place when the level of estrogen is lowered during a course of injections; it occurs after the withdrawal of progesterone during a course of injections. The onset of menstruation may be inhibited by other procedures. Progesterone, or testosterone, given immediately following any of the foregoing procedures but the last, inhibits the establishment of menstrual bleeding until the progesterone is withdrawn. Estrogen will delay the menstruation associated with ovariectomy, but not that which follows the withdrawal of progesterone. The common physiological denominator for all these various conditions is the state of the superficial portion of the endometrium. In addition to local conditions within the uterus which are responsible for the blanching, there are also periodic systemic changes of an as yet undefined nature which affect the sensitivity of the uterus to hormonic stimulation. Consequently, it appears unlikely that a "cause" for menstruation will ever be discovered; rather, it is more probable that a number of related and interdependent local and systemic conditions will be found indispensable in this phenomenon.

DANIEL G. MORTON, M.D.

Frank, R. T.: The Sex Hormones. *J. Am. M. Ass.*, 1940, 114: 1504.

The sex hormones are divided into two groups: (a) the prepituitary and prepituitary-like, and (b) the steroid (ovary, testis, adrenal, and placenta). The prepituitary and prepituitary-like hormones are of protein composition of unknown structure and act on the ovary and testis, while the steroid hormones have been isolated and their structure determined. These act on the muellerian and wolffian ducts in the immature, adult, and castrate subject.

The author points out that a permanent condition of chemical hermaphroditism persists throughout life in the human male and female. How great a rôle the sex hormones of the opposite sex play in physiology and functional pathology is as yet an open question. It is possible that they occur as intermediate metabolic products but that under certain conditions they may disturb the balance of sex sufficiently to produce symptoms.

An analysis of the blood and urine assays for normal and abnormal states is given by Frank, who believes that such assays have proved of great help in the evaluation of the various gynecological and obstetrical conditions encountered in practice, and the results of treatment of these conditions. A warning is sounded against considering every obscure condition as being of endocrine origin to the exclusion of anatomicopathological changes which are too often revealed by a routine physical examination.

Absence or decrease of the estrogens and/or of progestin causes functional disturbances in the female. Functional disturbances in the male are less well defined and are probably due to similar variations of androgen secretion. The steroid hormones when given in small amounts and for short periods stimulate prepituitary function; in large amounts and for long periods they inhibit it. In the female, estrogens are of use in the treatment of infantile gonorrhea and in almost every variety of menopausal disturbance. While they have been used in many other conditions, their effects have not been very convincing. Progestin relieves dysmenorrhea and may prevent abortion due to defective function of the corpus luteum of pregnancy. Androgens should prove of value in the treatment of castration symptoms in the male and are being tried in many other diseases. The gonadotropic factor of the anterior lobe of the pituitary gland is effective in cryptorchid patients.

ANTHONY F. SAVA, M.D.

Meaker, S. R.: Female Genital Hypoplasia. *J. Obst. & Gynaec. Brit. Emp.*, 1940, 47: 40.

The author notes that it is difficult to estimate the general incidence of hypoplasia of the female reproductive tract. Women, pregnant or parous, in whom the functional capacity of the organs has been demonstrated, show an almost negligible incidence of developmental arrests. In a series of 100 nulliparous women who sought relief for inflammatory conditions, the author found that 9 had uteri which presented the obvious stigmata of underdevelopment.

In development, the reproductive system remains stationary until the age of puberty when, normally, it manifests a second phase of differentiation, a phenomenon directly controlled by the endocrine glands. A deficiency of endocrine stimulus, due either to primary failure of the glands themselves or to a depressed constitutional state reacting unfavorably upon their function, may arrest development of the reproductive organs. Focal infections, congenital syphilis, anemia, disturbances of nutrition, and faults of hygiene may be exciting causes. Of 103 girls from sixteen to nineteen years old who had

delayed menarche or other disturbances of menstrual function, 61 were suffering from insufficiency of the anterior pituitary lobe. There were 11 cases of demonstrable thyroid failure, and, in 31 girls, non-endocrine constitutional depressions were present, anemia being the most frequent.

The complaint most often presented by genitally hypoplastic women is sterility. The important defect is an inadequate ovarian development. If pregnancy occurs, the miscarriage rate is high. Excessive bleeding post abortum or post partum is a complication always to be feared. Another symptom is dysmenorrhea of the spasmodic type. Since the hypoplastic myometrium retains an excessive proportion of connective tissue, uterine contractions which should be imperceptible become irregular, cramp-like, and painful.

In hypoplasia, the cervix is long, projecting as much as an inch into the vagina, and conical in shape. The os externum is of the pin-hole type. By histological study, there may be a proportion of connective tissue to muscle as great as 50 per cent, whereas in fully developed uteri, muscular elements predominate to the extent of about 90 per cent. Ovaries of the truly infantile type are long, narrow, and lobulated. After puberty they are likely to contain retention cysts—atretic follicles which represent abortive attempts at ovulation. Vulval hypoplasia always connotes an important developmental arrest in the internal organs, but the contrary is by no means true, since the majority of women with juvenile uteri show no vulval stigmata.

Using a new diagnostic sign defined by him as the uterine index, the author finds, following the study of a large amount of necropsy material, that in the average case the infantile index persists until the tenth birthday. Rapid development takes place during the thirteenth, fourteenth, and fifteenth years; and the adult index is attained at the age of nineteen.

As a rule, physical examination may give no evidence of retardation of uterine development. Most women whose genital organs are infantile appear in other respects to be perfectly developed. Some patients show stigmata of an earlier inadequacy; disproportion between trunk-length and limb-length, masculine distribution of hair, middle-third obesity, or breasts relatively lacking in glandular elements. These women seldom present the signs of an active endocrinopathy. During the critical period of adolescence, they may have passed through a transient phase of glandular derangement, followed soon by spontaneous readjustment of the endocrine balance. Such adult patients may be entirely free from symptoms of hormonal failure, but the imperfectly developed genitalia are a permanent residuum of old disturbances.

Attempts to treat genital hypoplasia in adults are discouraging for, after the age of twenty, the growth impulse is lost. Local treatments may do more harm than good. In certain cases, the growth impulse, appearing to be dormant, may be reawakened by the stimulus of a normal sex life. With pregnancy, further development of the organs is assured.

The recognition and prompt treatment of threatened or incipient genital hypoplasia in adolescent girls is important, for the growth impulse, though enfeebled or inhibited, is capable of being stimulated. Abnormal menstrual behavior indicates that development is not progressing as it should. Dysmenorrhea, irregular intervals, scanty flow, and secondary amenorrhea are obvious symptoms of subnormal function. Puberty bleeding results from deficient follicular activity, and in particular from a lack of the corpus-luteum hormone. Eighty per cent of white girls living in temperate climates have their first period before the fifteenth birthday, and 88 per cent before the sixteenth birthday.

The author states that a girl who has not established a regular, normal, and relatively painless menstrual habit before her fifteenth birthday requires a survey of her general health and her endocrine balance. If the delay extends to the sixteenth birthday, she becomes an emergency case, demanding thorough investigation and energetic treatment. Examination by rectum will assist in ruling out hermaphroditism, imperforate hymen, and incidental abnormalities. Both endocrine and non-endocrine disorders in the adolescent girl should be considered as factors capable of arresting genital development. The primary effect of endocrine therapy is replacement. The medication indicated most commonly is anterior pituitary lobe hormone, less often thyroid, and never ovary. Success depends upon accurate diagnosis, and upon the use of potent preparations in adequate dosage over a sufficient length of time.

Among non-endocrine constitutional diseases, there are two which require special attention: chronic focal infection and anemia. Chronic intoxication of whatever origin, especially from teeth, tonsils, or nasal sinuses, can exert upon the endocrine glands an inhibiting influence strong enough to depress normal function and to prevent the satisfactory results of organotherapy. Anemia is rather common in adolescent girls, and the milder grades often escape recognition; but the blood should be watched and treated on the slightest indication, since the effect of any anemia upon genital development is sometimes more harmful than would be suggested by the blood picture.

Two items in an ideal hygiene that bear so directly upon the well-being of adolescent girls are proper nutrition and a good balance between effort and relaxation. If the body suffers, no small part of the damage is likely to be visited upon the sensitive reproductive organs. HERBERT F. THURSTON, M.D.

Mihálkovics, E. von: Simple Puncture as Palliative Treatment in Pus Accumulations in the Female Pelvis (Die einfache Punktion als palliativ-therapeutisches Verfahren bei Eiteransammlungen des weiblichen Beckenraumes). *Monatsschr. f. Geburtsh. u. Gynaek.*, 1939, 109: 150.

After a review of the literature on the results of treatment of pelvic suppurations with simple punc-

ture, the author presents a critical examination of his own method and reports on his good experience with this simple treatment.

In view of the ever-present danger of fistula formation in more extensive opening of pus pockets in the regions of the tubes and ovaries, he suggests the substitution of the much simpler puncture method for that of colpotomy in all indicated cases. With such palliative treatment he reports good results in 68 of 100 cases. His success was greatest in early, unilateral cases which were not complicated with gonorrhea nor with abscesses in the pouch of Douglas. When sterile pus or serous exudate was obtained by the puncture the course of recovery was usually good. Such a puncture, however, does not necessarily indicate that there will be no recurrence. The results are not so good when various sites are punctured in order to open multiple abscesses. Lowering of the temperature was considered the criterion of successful treatment since leucocytosis and sedimentation rates were variable in their behavior and were not considered of prognostic value.

The advantages of the procedure, besides the nonoccurrence of fistula formation, are the immediate lessening of pain, shortening of the treatment period, the feasibility of reaching lateral and deeply localized pus pockets, and the shortening of the convalescent period. The author feels optimistic concerning the prognosis regarding later freedom from complications.

The punctures were repeated up to five times. Four times general disturbances occurred, such as singultus, vomiting, and chills. Nine times spontaneous perforation of rectal tumors occurred. Two patients died, one from an intercurrent severe kidney disease, the other from severe sepsis after diffuse thrombophlebitis of the pelvic veins.

On the basis of his experience the author concludes: (1) that colpotomy in cases of abscesses in the uterine adnexa is a poor procedure because of the danger of fistula formation, and is indicated only in cases in which there is acute danger to life; (2) that in fresh or exacerbated cases of suppuration of the adnexa, drainage of the pus by puncture is the best procedure for subjective betterment and for quickly lowering the temperature; (3) that simple emptying by means of puncture can be attempted even in abscesses of the parametrium and in infected hematoceles with expectation of success; and (4) that puncture can be substituted for colpotomy also in genital and extragenital abscesses of Douglas' pouch.

(Wolfram). Ronald R. Greene, M.D.

OBSTETRICS

PREGNANCY AND ITS COMPLICATIONS

Miller, H. E.: Ectopic Pregnancy: A Review of 137 Cases. *Am. J. Surg.*, 1940, 48: 47.

Miller presents a review of 137 cases of ectopic pregnancy that occurred at the Touro Infirmary, New Orleans, during the period of from 1924 to 1936. He reports the high uncorrected incidence of 1 extra-uterine to every 151 intra-uterine pregnancies (0.66 per cent) in New Orleans hospitals during this period. One hundred and thirty-four of the cases of his series were tubal in type, 2 were interstitial, and 1 was ovarian.

The usual theories of causation of ectopic nidation are briefly considered. Miller suggests that tubal obstruction plus a decidual response in the tubal mucosa, as a complementary influence, "would create a favorable soil for implantation in order for ectopic pregnancy to result." He comments on the percentage occurrence of ectopic pregnancies following suspension of the uterus and procedures purposed to relieve pelvic and abdominal adhesions. Only 4.6 per cent of his cases revealed pathological evidence of salpingitis; 81 per cent showed abnormal vaginal bleeding, while a history of amenorrhea occurred in 52.8 per cent. The most usual physical finding was tenderness in the lower abdomen (81 per cent). Findings in the blood count and smear reveal changes dependent on the amount and time of the intraperitoneal hemorrhage.

Miller is pessimistic regarding the diagnosis of unruptured ectopic pregnancy and states that it is "attended with the same luck which blesses the golfer who scores a hole in one." The diagnosis in all cases was made correctly in 47.2 per cent and highly considered in an additional 23.5 per cent.

The author believes there should be no expectant treatment for ectopic pregnancy and recommends immediate surgery. He adds that "the time for administration of fluids is during, or after, the control of the hemorrhage by ligature." The extent of the operative procedure must be regulated by the judgment of the surgeon and the condition of the patient. The excellent mortality of 2.18 per cent in 137 cases is reported. WILLARD G. FRENCH, M.D.

Reifferscheid, W., and Schmiemann, R.: Roentgenological Studies of So-Called Intra-Uterine Respiration of the Fetus (Roentgenologische Untersuchungen ueber die sogenannte intra-uterine Atmung des Feten). *Ber. d. phys.-med. Gesellsch. z. Wuerzburg*, 1939, 62: 202.

While repeating Ehrhardt's observations of intra-uterine drinking by the fetus, radiopaque shadows were observed in the region of the lungs. This observation became the basis of roentgenological observations of intra-uterine fetal respiratory movements which have been previously described by Ahlfeld, K. Reifferscheid and others. By means of injecting umbrathor into the amniotic fluid of women whose pregnancies had to be terminated because of medical indications, it was possible to deposit a contrast medium in the fetal lungs and to demonstrate it in the fetus while yet *in utero* by roentgenograms. By histological studies it was possible to prove that the umbrathor had been deposited in the lungs.

From these observations it can be said that the muscle contractions of the intra-uterine fetus occurring in rhythm with respiration, described by Ahlfeld, K. Reifferscheid and others, can be explainted roentgenologically as intra-uterine respiratory movements in which amniotic fluid is actively moved back and forth within the bronchial tree. The fetal respiratory movements could be demonstrated as early as the fourth or fifth month of pregnancy.

(W. REIFFERSCHEID). RULON W. RAWSON, M.D.

Jarcho, J.: Placenta Previa. Roentgen Diagnosis, Treatment, and a Technique for the Induction of Premature Labor. *Am. J. Surg.*, 1940, 48: 481.

Improved means of diagnosis have made it possible to recognize placenta previa at the first bleeding, and to distinguish partial and total previas in the cystogram. Roentgenographic studies will indicate the presence of monstrosities; also, the centers of ossification in the fetus reveal in advance whether it is viable. The knowledge thus obtained enables the accoucheur to choose the method of treatment best suited to the individual case, without loss of time and blood.

In inducing labor, the importance of stimulating its onset by making direct pressure upon Frankenhaeuser's great cervical ganglion is emphasized. The author presents a method of inducing labor based on this principle, and describes his technique, which he has employed for over twenty-five years, and which he believes should be considered in carefully selected cases and in some cases of placenta previa.

J. THORNWELL WITHERSPOON, M.D.

Portes, L., and Varangot, J.: Endometriosis and Pregnancy (Endométriose et gestation). *Gynéc. et obst.*, 1939–1940, 40: 298.

Portes and Varangot note that the association of endometriosis and pregnancy is rare, because women with endometriosis are frequently sterile and because endometriosis occurs most often in the fifth decade of life, an age at which pregnancy rarely occurs. In the case reported, the patient was a woman thirty-two years of age, in the seventh month of her second pregnancy. She had had no unusual symptoms, but a midwife, on making a vaginal examination, found blood. The patient was sent to the hospital at once and examination with the speculum showed a tumor that bled easily in the right lateral vaginal cul-de-sac. A histological examination at that time led to the

diagnosis of spinocellular epithelioma of the vagina. The patient was delivered by cesarean section followed by supravaginal hysterectomy. Four days later, a second biopsy showed a typical endometriosis of the vagina. The patient made a good recovery and three months later showed only a cicatricial lesion in the right lateral cul-de-sac, extending downward in the vagina; it was painless and there was no discharge.

On re-examining the first biopsy specimen, it was found that the cellular formation that had been wrongly interpreted as epithelioma was in reality due to a transformation of the glandular elements and stroma of the endometriosis, of a decidual nature corresponding to that taking place in the normal endometrium in pregnancy. The intensity of this reaction had caused an enlargement of the tumor, which ulcerated and bled. After delivery, the tumor showed the typical characteristics of endometriosis. This case shows that endometriosis in association with pregnancy may lead to errors in diagnosis and may cause unexpected and serious complications because of the reaction produced by pregnancy in all endometrial tissue.

In a review of the literature, the authors find that the most usual sites of endometriosis associated with pregnancy are the uterus and the rectovaginal septum. In cases of uterine endometriosis in pregnancy, the tumor sometimes causes no symptoms, and is found only when the patient is delivered by cesarean section. More frequently the endometriosis is incorrectly diagnosed as a myoma. In other cases the uterine endometriosis, because of its reaction to pregnancy, may cause rupture of the uterus by infiltrating and breaking down the myometrium; or it may cause severe uterine hemorrhage.

Endometriosis of the rectovaginal septum may cause few or no symptoms during pregnancy and no serious obstacle to normal delivery. In other cases, the location and size of the tumor may make cesarean section necessary, followed in some instances by hysterectomy. Only 2 cases were found reported in which endometriosis in a pregnant woman was not situated either in the uterus or the rectovaginal septum—1 was a case of ovarian endometriosis and the other a case of endometriosis in the scar of a previous cesarean section.

The transformation that occurs in endometriosis in pregnancy should be better understood in order to avoid mistakes of diagnosis. The review of the literature indicates that endometriosis is most frequently found in association with pregnancy in elderly primiparas. ALICE M. MEYERS.

MISCELLANEOUS

Thomas, R. C.: Three Thousand One Hundred and Forty-Four Consecutive Deliveries Without a Maternal Death Due to Pregnancy. *Brit. M. J.*, 1940, 1: 562.

The Croydon Obstetrical Service, between January 3, 1938, and June 4, 1939, conducted 3,144 consecutive deliveries after the twenty-eighth week, among which a maternal death attributable to pregnancy has not occurred. (One mother died of pneumococcal pneumonia and empyema, the cause of death being confirmed by post-mortem examination. She had been ill for seven days before she was delivered, on the last day of her illness, of a thirty-eight weeks' live baby, after a labor of about six hours. This was the only death among the deliveries in this series, and was not attributable to pregnancy.)

In the following table are shown some of the major abnormalities treated, together with cesarean sections and forceps deliveries:

Placenta previa	41
Accidental hemorrhage	23
Hydramnios	26
Eclampsia	4
Toxemia, including all cases of albuminuria and/or hypertension	389
Shoulder presentation	10
Prolapsed cord	9
Forceps deliveries	94
Cesarean section	74

Among the 3,144 deliveries, there were 32 sets of twins and 1 set of triplets. The total number of infants born was therefore 3,178.

The number of maternal and fetal abnormalities and macerated fetuses associated with the 92 still-births are here given:

Macerated	28
Anencephalic	7
Hydrocephalic	10
Achondroplastic	2
Spina bifida	3
Placenta previa	6
Accidental hemorrhage	4
Toxemia	11
Eclampsia	3
Hydramnios	8
Shoulder presentation	7
Prolapsed cord	5
Blackwater fever	1
Twin pregnancy	4

Among the 78 still-births which occurred in the two hospitals there were 26 premature fetuses, taking the weight of 5 lb. 8 oz. or less as the standard of prematurity. In every case except 1, abnormalities, fetal or maternal, or both, were found.

The infant deaths among the 3,086 live births numbered 43. The infant death rate for the Service is therefore 13.9 per 1,000 live births.

Among the 38 neonatal deaths there were 26 premature infants. As in the still-births, maternal and/or fetal abnormalities were present in many instances.

J. THORNWELL WITHERSPOON, M.D.

Stroink, J. A.: The Diagnosis and Treatment of Mole Pregnancy and Chorio-Epithelioma (Ueber die Diagnostik und Behandlung von Molenschwangerschaft und Chorionepitheliom). *Nederl. Tijdschr. v. Verlosk.*, 1939, 42: 279.

In the Utrecht Klinik from 1927 to 1939 there were treated 28 patients with moles of pregnancy. Twenty

of the women came from the out-patient clinic. In 23,000 births occurring in the twelve years considered, the frequency of moles of pregnancy amounted to 1:1,150. Two of the 28 patients (7 per cent) developed a chorio-epithelioma. Seven patients were admitted after the mole of pregnancy condition on account of bleeding or infection; 2 of these had a chorio-epithelioma. Eight patients were admitted with chorio-epithelioma without previously having exhibited a mole of pregnancy.

Today the Aschheim-Zondek reaction with diluted urine is the method of choice for the diagnosis of moles of pregnancy. A urine diluted 500 times still gives a positive reaction. Except for the cases in which a marked amount of bleeding occurs, expectant treatment will have advantages. The spontaneous expulsion of the mole was awaited in 24 of the 28 cases; 1 time a removal of the uterus was carried out; 1 time birth was produced by cervical tamponade, and 2 times, because of a severe hemorrhage, the mole was manually removed. In the 24 cases in which the spontaneous expulsion of the mole was awaited, retained portions were removed 2 times manually and 1 time by means of the curette. All 28 patients recovered.

In 23 cases it was determined at what time after expulsion of the mole the Aschheim-Zondek reaction became negative. This occurred within two weeks in one-third of the cases, within three weeks in two-thirds of the cases, and within four weeks in five-sixths of the cases. In the patients in which the Aschheim-Zondek reaction was not negative within a month a curettage was done to remove retained small portions of the mole. After the curettage the Aschheim-Zondek test became negative within one week and remained so thereafter. In the 4 cases of chorio-epithelioma after the mole pregnancy, the Aschheim-Zondek test remained positive. After curettage a chorio-epithelioma gives a somewhat equivocal microscopic picture. The diagnosis of chorio-epithelioma in these cases can be established even some time later since the Aschheim-Zondek test remains positive or after a time in which it was negative it becomes positive again. For half a year the Aschheim-Zondek reaction was used for control. The treatment of chorio-epithelioma consists in the combination of operation and x-ray therapy. Since by means of x-ray therapy alone a few patients will be cured, x-ray therapy (in carcinoma doses), therefore, seems to play the more important part according to the author.

The case histories of the 12 patients with chorio-epithelioma follow in chronological order. In 4 patients a chorio-epithelioma occurred after a mole pregnancy, in 8 without a previous mole pregnancy. The last 8 cases were all involved with metastases. Six of the 12 cases ended in recovery and 6 in death.

In the discussion VON ENGELHARD and MULLER advanced opinions against the expectant treatment. DESNOO, who formerly likewise treated these cases actively, at present favors conservative therapy.

(PUETZ). JOHN R. PAINE, M.D.

GENITO-URINARY SURGERY

ADRENAL, KIDNEY, AND URETER

Firor, W. M.: The Treatment of Addison's Disease by the Implantation of Synthetic Hormone. *Ann. Surg.*, 1940, 111: 942.

The clinical syndrome of Addison's disease has been known for eighty-four years; its pathological physiology only ten years; and the crystalline substance curative of its symptoms only two years. In this article are well presented the historical milestones of the growth of our understanding of this disease since the time of Addison.

The immediate impetus to this paper was given by (1) the isolation of the synthetic hormone by Steiger and Reichstein, and (2) by the work of Thorn of the Johns Hopkins Hospital, Baltimore, Maryland, who maintained bilaterally adrenalectomized dogs on single daily injections of desoxycorticosterone acetate despite a low sodium-chloride and high potassium diet. Subcutaneously implantation of sufficient pellets of the crystalline hormone maintained these animals equally satisfactorily. Cessation of the daily injections or removal of the pellets induced a clinical syndrome identical with that of Addison's disease. Pellet implantation was 25 per cent more efficient than daily injections in oil.

Since September, 1938, Thorn and the author have treated 17 patients at the Metabolic Ward of the Johns Hopkins Hospital by pellet implantation. Daily requirements were first established by adding 10 gm. of sodium chloride to the basal state of the patient and then giving daily injections of from 2 to 10 mgm. of "percorten" according to the patient's needs. Evidence of adequate therapy was taken to be the maintenance of (1) optimum body weight, (2) normal blood pressure with normal plasma volume, (3) positive sodium and chloride balance, and (4) the normal concentration of plasma electrolytes. When the daily requirement was determined the injections were stopped and pellets implanted on the basis that each 125 mgm. pellet was equivalent to 5 mgm. of the hormone in oil daily.

Implantation is done in the infrascapular region under procaine anesthesia with rigid asepsis. Incisions are made in the subcutaneous fat and 10 or 12 radial pockets made by blunt dissection. Hemostasis is completed and the pellets are introduced with a nasal dilator. In the author's group of 17 patients all have been successfully maintained on pellets alone from four to nine months. All but 2 have resumed their former activities fully. Every patient has gained weight, shown improvement in blood pressure, maintained a positive sodium and chloride balance, and the blood volume determinations have returned to normal. No untoward effects have been reported. All wounds have healed promptly and painlessly; no pellets sloughed out. None of the patients has developed hypertension, a fact attributed to the carefully computed daily requirements. In 1 patient partial regeneration of cortical tissue is suspected.

The author concludes with the words of warning that improperly prepared pellets will crumble and greatly increase the rate of absorption and that sterilization of the pellets as now practiced with hot acetone solution of the crystalline hormone, Seitz filtration, and, finally, low-pressure steam sterilization, is still very imperfect. Finally, it must not be forgotten that pellet implantation does not obviate the necessity for simultaneous careful clinical supervision. STANLEY ROBBINS, M.D.

Korenchevsky, V., and Ross, M. A.: Kidneys and Sex Hormones. *Brit. M. J.*, 1940, 1: 645.

These authors report a study on the kidneys of intact and castrated rats receiving various male and female sex hormones.

They report that gonadectomy in males produces small "castration" kidneys. This did not follow in females. In both normal and gonadectomized female rats and castrated males the male hormones produced true hypertrophy of the kidneys. Except for pathological changes produced in the kidneys of normal females by large doses, the action of testosterone esters on these organs appears to have no harmful effect. Estrogens in certain doses produced peculiar cyst-like degenerative changes in the kidneys mostly confined to the boundary layer of the cortex and medulla. RULON W. RAWSON, M.D.

MISCELLANEOUS

Lima, E. J.: The Action of the Derivatives of Sulfanilamide in the Treatment of Lymphogranulomatosis Inguinalis (Acción de los derivados de la sulfamina en la enfermedad de Nicolas-Fabre). *Bol. y trab. Acad. argent. de cirug.*, 1940, 24: 11.

Lymphogranulomatosis inguinalis was first recognized as a venereal disease and a clinical entity by the German school (Frei and Koppel). This disease shows all the symptoms of the venereal diseases: lesions on the skin, mucous membranes, lymphatic system, and nervous system. It resembles syphilis in that it has as a first manifestation chancre and inguinal gland involvement. The most important symptom for diagnosis is the positive reaction of Frei. The author thinks this reaction can be compared favorably with the Wassermann reaction, and that a negative reaction, after long treatment, is a good sign of cure of the disease.

Negativity of the Frei reaction, as the result of treatment, is very seldom found and, for this reason, the disease can be considered much more serious than syphilis. Its manifestations are also rebellious to treatment and they follow the same course as those of syphilis. Therefore, there is first a primary

period with little chancres, without infiltration, with gland involvement, and a positive Frei test. The secondary period brings cutaneous lesions with rectal and vulvovaginal complications. The tertiary period is one of latency. If good treatment produces a negative Frei reaction, the author does not accept this as a cure till the clinical signs disappear also.

The treatment with the sulfanilamide derivative (prontosil) was made with all the necessary precautions against the general toxic complications: headache, asthenia, polyneuritis, and the toxic local complications (gastric, hepatic, cutaneous, nervous, and renal).

Prontosil was given per os and as injections (15 c.cm. of 5 per cent solution). In three weeks the patient has been given the full dose of medicine. As an example, in a patient of 60 kgm. weight, the substance is given as follows:

First week: 0.05 gr. for each kgm. of weight, 3 gr. a day for seven days, so as to total 21 gr. the first week.

Second week: 0.04 gr. for each kgm. of weight, 2.40 gr. a day, a total of 16.80 gr. in the second week.

Third week: 0.03 gr. for each kgm. of weight, 1.8 gr. a day, a total of 12.60 gr. in the third week.

The full dose is 50 gr.

After the first treatment one can see a modification of the inguinal condition (which sometimes regresses spontaneously), but the rectal and genital lesions and the Frei reaction do not change at all. As one might think that the action of the sulfanilamide was upon the infection, the author combines this treatment with the necessary treatment of the general state of the patient. He treats also the determining causes of the disease, trying to obtain sterilization with gold, copper, sodium-iodide, and sulfanilamide in successive series, and treats the local lesions, which are greatly improved by the combined general treatment. Each treatment is followed by a period of rest, after which new alternative injections of the same drugs are made for a three-week period. HECTOR MARINO, M.D.

CORRECTION

Palecsko, I.: Prolapse of the Ureter (Ueber den Harnleitervorfall). *Arb. chir. Klin. Univ. Pécs*, 1939, p. 103.

In the abstract of this article which appeared on p. 154 of this volume, the word "ureterocele" should be substituted for the word "urethrocele."

SURGERY OF THE BONES, JOINTS, MUSCLES, TENDONS

CONDITIONS OF THE BONES, JOINTS, MUSCLES, TENDONS, ETC,

Campbell, A. M. G.: Carcinomatosis of Bone: Difficulties in Diagnosis. *Lancet*, 1940, 238: 777.

Five cases of carcinomatosis of bone are discussed, in all of which an original diagnosis of rheumatism was made. Later studies proved them all to be secondary or metastatic carcinoma from a primary tumor which had given no symptoms.

Pain, anemia, and the radiological findings lead to the diagnosis, but in the early stages the latter two may be negative. The possibility of metastatic carcinoma must be borne in mind in unexplained bone and joint pains in older patients. Repeated roentgenograms and prolonged observation is advisable in obscure cases. CHESTER C. GUY, M.D.

SURGERY OF THE BONES, JOINTS, MUSCLES, TENDONS, ETC.

Costantini and Kehl: Arthrodesis in Tabetic Arthropathies (Pour l'arthrodèse dans les arthropathies tabétiques). *Presse méd.*, Par., 1940, 48: 308.

Arthrodesis has not been an accepted method of dealing with the flail joints of tabes, principally because it was believed that tabetic bones had little power of regeneration. Rare cases have been reported with success, but as a rule French surgeons have discouraged any attempt at surgery. The authors point out that, whereas the attitude may have been justified before 1914, there is much better outlook today. The principal reason for being more optimistic is the very much improved treatment of syphilis. They also argue that the observations of Leriche on improved osteogenesis in the presence of hyperemia produced by sympathectomy have not been taken into consideration; and the hyperemia of tabetic extremities is probably similarly on a neurogenic basis.

Their first attempt at arthrodesis in a Charcot knee joint of a bedridden patient was entirely successful. The arthrodesis was accomplished by means of a thick tibial graft from the opposite leg. The same year another knee was ankylosed in a similar manner. There is a chronological history of successful arthrodeses on tabetic joints. Much is made of a successful extra-articular arthrodesis of the hip by Mathieu. The article deals at some length with the idea that because of a few disappointing results in the surgical treatment of these joints in former days, surgeons have not been sufficiently energetic in their treatment. At present, the improved technique of arthrodesis, especially with use of the Albee graft, combined with improved treatment of the underlying conditions in the patient, make the outlook for successful surgical intervention much more hopeful. ADRIEN VERBRUGGHEN, M.D.

Orell, S.: Osteosynthesis in Resection of the Knee-Joint (À propos des ostéosynthèses dans les résections de l'articulation du genou). *J. internat. de chir.*, 1940, 5: 147.

In cases of resection of the knee by the Waldenström method in which only the fibrous tissues of the joint are sutured and the limb is immobilized in plaster, Orell has found that results are not always satisfactory. He prefers some method of osteosynthesis. At first he used a straight bone graft, pointed at one end; the pointed end was introduced into the spongy bone of the tibia, the opposite end into the femur, and the knee was placed in a plaster cast immediately after operation, but the foot left free.

While very satisfactory results were secured by this method, including 6 cures without complications in 10 cases of tuberculosis of the joint, the author has sought to improve the results and avoid complications by the use of a curved bone graft (os purum). The major part of this graft is of compact bone, but spongy bone forms the convex surface. This graft is also pointed at one end. After resection the tibia and femur are held in the correct position, and a specially designed perforator of the same shape as the bone graft is employed to form a channel in the femur and tibia, with the aid of a few blows from the surgical hammer. The perforator is withdrawn with the use of an iron instrument. The bone graft is placed in this channel with the pointed end in the spongy bone of the tibia; a special guide of bakelite is used to facilitate the placing of the graft. The

Fig. 1.

knee is then immobilized in a plaster cast. In this way solid osteosynthesis is obtained, the spongy bone of the concave surface of the graft adhering closely to the spongy bone of the tibia and femur.

It is important that the graft of os purum be thoroughly dry when introduced into the bony channel prepared for it. It is boiled in physiological saline solution the afternoon of the day before it is to be used, and dried overnight either in sterile gauze at room temperature or by dry heat at 50° or 60° C. The author has treated 6 cases, 5 cases of tuberculosis of the knee-joint and 1 case of gonorrheal arthritis, by resection of the knee-joint, followed by the use of the bone graft described. The results in 4 of these cases were excellent; in 2 cases there were complications due to infection of the soft parts; the bone graft in these cases, however, was firmly fixed in position. ALICE M. MEYERS.

FRACTURES AND DISCLOCATIONS

Hermann, O. J.: Compound-Fracture Therapy at the Boston City Hospital. *Arch. Surg.*, 1940, 40: 853.

An outline is given of the steps taken in the care of a patient with a compound fracture from the time he is admitted to the Hospital. The technique of wound cleansing and débridement is discussed.

The use of internal fixation is not contraindicated and does not contribute to the development of sepsis. The puncture type of wounds should be débrided in the same manner as the more extensive soft-tissue wounds. In the closure of the wound, either the open or closed method may be used. In the treatment of compound fractures the surgeon should be open-minded and vary his technique as the case requires. Bone grafting may save much time in cases of delayed union.

The treatment of gas-bacillus infections and tetanus is also discussed. CHESTER C. GUY, M.D.

Guilherme, E.: Some Notes on the Treatment of Recent Compound Fractures (Algumas notas acerca do tratamento das fracturas abertas recentes). *Rev. brasil. de orthop. e traumatol.*, 1940, 1: 291.

During 1937, Guilherme and his collaborators treated 101 cases of recent compound fracture by careful excision of the focus. Six patients died; 2 died from septicemia and 1 from gas gangrene, and 3, who had compound fractures of both legs, died within twenty-four hours after the operation. Guilherme warns that the method can be used only by experienced surgeons who are in a position to judge correctly the degree of vitality of the involved soft tissues. There are two problems in the treatment of open fractures: the surgical treatment of the soft tissues, upon which depends the immediate prognosis, and the orthopedic treatment of the bone lesions, which is responsible for the remote results.

Excision of the skin and the subcutaneous cellular tissue offers no difficulties even in extensive injury because all pockets can be found and kept clean by the judicious use of counteropenings for drainage. However, difficulties arise when the aponeurotic wound is excised and an irregularly destroyed or ischemic muscular mass is found, because this tissue is always the starting point of gas gangrene or of gangrenous phlegmon. Individual experience is indispensable in these cases, as shown by the personal statistics which improve gradually with the lapse of time.

It is always necessary to perform the excision so as to leave a muscular stump of living, bleeding tissue, presenting a healthy aspect. The nerves must be respected and eventually reconstructed, and the principal vessels must be saved. There is only one contraindication to excision, which is then replaced by amputation: destruction of the principal artery or of the large nerves. The only excuse for removal of bone splinters is when they are found far from the focus of fracture. In principle, all bone fragments should be replaced in position, especially those provided with periosteum, and osteosynthesis should not be used. At most, a catgut ligature may be passed around them; they are kept in position by the reducing traction.

Whenever reconstruction is possible, the skin only should be sutured; tension on the sutures may be prevented by parallel incisions and moderate undermining of the subcutaneous cellular tissue. When suture is impossible, the wound is allowed to granulate under the plaster cast. A compress is placed over the wound. *Focal* and *perifocal* mixed serum therapy against tetanus and gas gangrene is given before the cast is applied.

No padding is used under the plaster cast which must provide strict immobilization and be extensive; in open fracture of a lower extremity a cast should be applied to each of the extremities and the casts should be connected or joined by transverse bars.

The principle of infrequent dressings must be observed. From the beginning, the cast will be stained with blood and may even be soaked with it; if hemostasis has been well controlled at the time of the operation, the temptation to open the cast in order to discover the source of bleeding must be resisted.

It is always possible to obtain reduction by means of Kirschner pins passed through the bone. The member must be kept elevated in order to avoid the development of edema. The course of calcification is followed roentgenographically. Usually, the plaster cast can be removed from the lower extremity after from sixty to seventy days, and from the upper extremity after from thirty to forty-five days; at this time, the wound is generally found to be healed without maceration of the scar.

RICHARD KEMEL, M.D.

Buermann, E.: Fractures of the Head of the Radius (Die Brueche des Radiuskoepfchens). *Arch. f. klin. Chir.*, 1939, 197: 115.

After a review of the literature, which demonstrates the inadequate state of our knowledge of

fractures of the radial head, the anatomy and physiology of the elbow joint are described. The author has treated 52 cases of his own. Forty-three of these resulted from direct trauma, 7 from indirect. In 2 the form of trauma was not clear. The 7 injuries resulting from indirect trauma were 7 fractures and 1 crack fracture. Among the 43 indirect injuries there were 23 fractures, and 20 fissures and cracks. The average age of the patients was thirty-six years. The indirect injuries resulted from falls on the palm of the hand. In the 52 injuries there were no other complicating fractures.

Five types of fracture are differentiated for the purpose of treatment: (1) incomplete fracture of the head; (2) complete fracture of the head; (3) incomplete fracture of the neck; (4) complete fracture of the neck; and (5) fracture of the head and epiphyseal injury in children. Every single type of fracture falls into this classification. The 52 cases treated by the author are tabulated.

The following symptoms are diagnostically important: painful restriction of rotary motion especially in the direction of supination; restriction of flexion and especially of extension of the elbow joint; and local tenderness to pressure and also to percussion by an axial blow on the radius.

The author agrees with recent observers and recommends closed treatment whenever possible, but otherwise operative treatment. The removal of the radial head gives unsatisfactory results. Boehler and Pfab have always found permanent disturbances of function following this method. The author treated only 3 of his 52 patients by operative methods, all 3 having suffered direct trauma.

The fractures due to indirect trauma are for the most part more serious. Oppolzer has maintained that fractures of the radial head in children should always be reduced by closed methods. Under ethylchloride anesthesia the forearm in forced extension is brought into varus, the operator using his thigh as a fulcrum. A simultaneous pull is made on the forearm and the joint space opens. By a pressure with the thumb from the lateral side the displaced head is brought back to its original situation. Immediately the forearm is slowly pronated and the elbow flexed. Immobilization is maintained for from two to three weeks in a dorsal unpadded plaster slab; following this, hot soaks are administered and active exercises are prescribed.

The author states that in retrospect his treatment is to be regarded as partly poor, as is shown by the average incapacity period of forty-six and four-tenths days and the average treatment period of seventy-nine and four-tenths days. Among the 24 cases treated from 1932 to 1935 with soothing ointments and after a few days with occupational therapy, 17 cases with disturbances of function have remained. Of the 28 patients treated with immobilizing bandages since 1936, only 7 have persistent disturbances of function. Immobilization for at least two weeks is indicated.

(Buettner). Richard Warren, M.D.

Scaglietti, O.: The Present Status of the Treatment of Congenital Dislocation of the Hip (Indirizzi odierni nel trattamento della lussazione congenita dell'anca). *Chir. d. organi di movimento*, 1940, 25: 308.

The author presents a review and statistical analysis of the cases of congenital dislocation of the hip in Italy. Of the total number of 15,272 cases, 12,747 (83.46 per cent) were found in females and 2,525 (16.53 per cent) in males; thus the ratio of males to females was 1 to 5.04. Dislocation was unilateral in 8,226 (57.13 per cent) and bilateral in 7,046 (46.13 per cent). Of the unilateral cases, 65.6 per cent were on the left side and 34.33 per cent were on the right side. According to the geographical distribution, it was found that the condition occurred more frequently in northern than in southern Italy and less frequently in the mountainous regions than in the plains.

At the Rizzoli Institute, 777 cases were treated by simple abduction, 3,628 cases by the Paci-Lorenz non-operative method, and 176 cases by operative reduction. Of the first group of 777 cases, 736 (94.71 per cent) were diagnosed and treated during the first twelve months of life. Treatment consisted of progressive reduction by maximum abduction and internal rotation according to the principles of Putti. The author used the apparatus of Forrester and Brown. The average duration of treatment was from seven to nine months. Of these cases, 478 were followed up and examined clinically and radiologically. The fact that excellent results were obtained in 93.92 per cent of them shows the importance of early treatment, as previously emphasized by Putti.

In the group treated by the non-operative Paci-Lorenz method, good results were obtained in from 45 to 50 per cent. The author states that poor results according to Putti were due to two types of causes: mechanical and biological.

From 1899 to 1938, 176 (3.52 per cent) of 4,990 cases of congenital dislocation treated at the Rizzoli Institute were treated by operative reduction. The technique of Putti and Zanoli was employed. Of this number, 86 cases had been treated previously without success by non-operative methods, 24 had presented recurrence, and in 66 primary operative therapy was considered preferable either because of age or anatomical conditions. Forty-nine cases were followed up; of these 5 were bilateral. Good results were obtained in about 25 per cent.

The author then briefly reviews the results in the statistics presented by Gill in America, Leveuf in France, and Schede in Germany.

He emphasizes certain rules for non-operative reduction which he states are well known. Various other important factors in the treatment are briefly reviewed. He calls attention to the fact that the operative method of therapy will give better results than the non-operative method and that one of the most important factors in obtaining good results is early recognition and treatment.

Michael DeBakey, M.D.

Da Costa Bomfim, R.: Monteggia's Fracture; 2 Cases: Posterior and Anterolateral Dislocation (Fractura de Monteggia; a proposito de dois casos: luxação posterior, luxação antero-lateral). *Rev. brasil. de orthop. e traumatol.*, 1939, 1: 18.

Isolated fracture of the diaphysis of the ulna is rare. When after a traumatism the ulna is found to be fractured and the radius intact, the latter should be suspected of dislocation of its upper extremity. Fracture of the diaphysis of the ulna and simultaneous dislocation of the head of the radius constitute Monteggia's fracture, which is characterized by a high incidence of bad functional results, because the dislocation is often unrecognized. Da Costa Bomfim describes 2 cases which he treated successfully.

Monteggia's fracture, while rare, is not exceptional. The diaphysis of the ulna is usually fractured in its upper third, occasionally in its middle, and very seldom in its lower third; if the fracture occurs in the coronoid process or in the olecranon, it should not be classified as a Monteggia fracture. The simultaneous dislocation of the radius is nearly always anterior or anterolateral; posterior dislocation, as in the author's first case, is rather rare. Three mechanisms are considered in the production of Monteggia's fracture: (1) a direct and most frequent one, in which there is a violent injury of the posterior aspect of the forearm; (2) a direct-indirect one, in which the patient falls on uneven ground, suffers a direct fracture of the ulna at the point of impact, and on rising dislocates the radius by violent pull of the biceps; and (3) an indirect-direct one, in which the patient falls on the palm of the hand and suffers a direct dislocation of the radius by the impact of the forearm on the ground, and an indirect fracture of the ulna. The last two mechanisms should be called indirect.

Careful examination will often lead to the correct diagnosis, but extreme pain may prevent the maneuvers necessary to make a complete investigation; besides, edema may mask the landmarks of the region. In these cases the patient may be anesthetized to allow adequate examination. Frontal and lateral roentgenograms are indicated, the first with the forearm in extension, and the second with the forearm in flexion at an angle of about 90 degrees and in supination with the thumb directed upward.

Early reduction is necessary and with correct technique will nearly always be possible within the first hours without surgical intervention. Reduction should also be tried if the patient is seen several days after the accident; in old lesions, surgical methods are considered advisable. The author's technique includes:

1. Disinfection of the area with iodized alcohol and the injection of 25 c.cm. of a 2 per cent solution of novocaine into the hemarthrosis and of 20 c.cm. into the hematoma of the fracture.

2. With the patient in dorsal decubitus, the arm abducted in horizontal position and the forearm flexed to a right angle, counterextension is applied to the arm just above the elbow.

3. The corresponding hand of the surgeon grasps the hand of the patient and exerts a gradual, strong traction, while the other hand embraces the forearm and with the thumb verifies progress and guides the head of the radius in front of the condyle. When the ulna is reduced, its curvature is corrected by counterpressure and the course of the radial head is verified under movements of pronation and supination.

4. A snapping sensation reveals reduction of the dislocation, and pronation and supination become ample and free.

5. Under continuous traction, flexion of the forearm is increased to stabilize the reduction, and the alignment of the fracture is again verified.

6. An assistant continues the traction while the plaster cast is applied with the forearm flexed at a right angle or more, in pronation, and with the thumb pointing upward. A posterior plaster splint is applied directly on the skin from the axilla to the wrist, including the cubital border of the hand; the anterior aspect is protected by a slight layer of cotton wool from the arm to the wrist, and the splint is completed with a few circular turns of plaster bandage. If the hemarthrosis is serious, it is advisable to put the arm in abduction to the horizontal in order to favor the circulation. The after-treatment consists of active movements; the patient should be taught to try to move the blocked joints even during immobilization, in order to maintain the tonus of the periarticular muscles and to prevent stiffness.

In old cases with faulty consolidation of the fracture, osteotomy is indicated and bloodless reduction of the radius is first tried; if this fails, open reduction is necessary. Resection of the head of the radius is done and always decreases the serious limitation of movements of the elbow. RICHARD KEMEL, M.D.

Vidal, F. J.: Gunshot Fractures of the Femur. Experiences from the Spanish War (Oberschenkelschussbrueche—Erfahrungen aus dem spanischen Krieg). *Chirurg*, 1940, 12: 70.

Six hundred gunshot fractures of the femur were treated following the principles of Boehler and Schueler. As initial treatment on the field, the Cramer splint has proved the best. The wounded men with emergency dressings arrived at the classifying ambulance station lying 20 or 40 km. behind the front. All the gunshot fractures with small ingress and outlet shrapnel wounds were treated with strict conservatism, and they healed like closed fractures. All the others were operated upon.

The author advises excision of the skin and other wound care. There should be no forceful removal of large splinters, no chemical disinfection, and no suturing. He finds a plaster case, including the pelvis, in the Boehler screw-traction dressing the best form of transport dressing. The limb is maintained with a small amount of mobility in the knee and hip joints. Blue crayon is used for writing details on the dressing for the subsequent case history. After this the patient is brought to the central

military hospital, about 200 km. behind the front, in about nine hours; so that the wounded come under definitive treatment on an average after twenty-four or forty-eight hours. Each bed has a Boehler thigh splint, a wooden step for elevating the foot of the bed, two 5 kgm. weights, a stand on which the limb may be rested when in maximal abduction, support for the well foot, and a traction stirrup. The splint is removed, roentgen exposures are taken in two planes, and permanent traction is applied: 1.5 mm. of thick non-rusting steel is passed through the tibial tuberosities with an electric drill without local anesthesia; the wire is made taut in a Boehler or other form of stirrup; and, finally, the anterior part of the foot is suspended from the apparatus by an adhesive plaster dressing. Thirty cases of gunshot fracture of the thigh could be handled in this manner during a forenoon.

The wounds receive open treatment after the method of Vincenz von Kern; all further operative procedures are carried out in bed under continuous traction, which remains in force, as a rule, for six weeks. Three or four weeks after the start the continuous traction is carried on by a supracondylar pin. Following the six weeks of continuous traction, if the wounds are in the process of healing, the patient is usually put up in a pelvic plaster cast with extension of the thigh, and a walking iron stirrup. A few weeks later a circular plaster splint is applied, the plaster being worn for an average of two and one-half months. The entire period for consolidation of the fracture therefore takes a total of four months. There are, however, instances in which the plaster must be worn for six months or longer. Roentgen control is necessary every eight to fourteen days at first. Adhesive dressing is used after removal of the cast and then after fourteen days, approximately, this is removed and the patient is granted sick-leave with instructions to practice movement, above all, to keep the joint moving. Although physical therapy was not practiced at all, the results were very good. The author never practiced early removal of shell splinters; many of these came out because of suppuration, others were later found included in an abscess. Sequestra were never removed earlier than six months after the first dressing.

Of 600 patients with gunshot fractures of the femur, only 22 (3.6 per cent) died; 1 of tetanus, 3 of gas gangrene, 6 of hemorrhage, and 12 of sepsis. In this connection it is interesting to note that the author himself admits that he was perhaps too conservative, as earlier amputation might have saved a life in some cases, although he did 2 amputations for gas gangrene and 8 for sepsis. Among the 578 patients who remained alive, there was not a single instance of amputation and not a single example of pseudarthrosis. Shortening of more than 3 cm. was present in only 1 patient, who had a shortening of 5 cm. This patient, however, did not receive care in the author's station but at another. In 4 of the 6 patients who died of hemorrhage, the femoral artery was the vessel involved; in the 2 remaining, the profunda. Of the patients who died of sepsis, 3 had coincidental suppuration of the knee as a complication. It is to be emphasized that the station in the first twenty-one months had only 1 death from sepsis; the 11 other deaths occurred in the last five months, 6 in the last month during the mass emigration. The author ascribes the incidence of death in the last periods to the poor nutritional care and poor transportation facilities.

(Franz). John W. Brennan, M.D.

SURGERY OF THE BLOOD AND LYMPH SYSTEMS

BLOOD VESSELS

Holling, H. E.: The Etiology of Vascular Symptoms Occurring in Cases of Cervical Rib. *Guy's Hosp. Rep.*, Lond., 1939, 89: 285.

Symptoms caused by a cervical rib may be either nervous or vascular. The nervous symptoms result from pressure of the rib on the brachial plexus. The origin of the vascular symptoms remains in doubt. Interference with the blood supply may arise from pressure of the rib either on the subclavian artery or on the vasomotor fibers to the arm. The relative importance of these two factors is in dispute.

Two cases of cervical rib showing vascular symptoms are described. Both were greatly relieved by removal of the cervical rib. In the first case, there was a cervical rib on the right side with vascular changes in the hand. Obstruction to the blood supply of the arm occurred whenever the arm was abducted. At operation it was found that intermittent arterial obstruction was caused by compression of the subclavian artery between the cervical rib and the clavicle. Following the removal of the rib, the circulation to the right arm steadily improved. In the second case, a cervical rib on the right side caused marked disturbance of the arterial supply to the arm and gangrene of the terminal portion of the thumb. At operation, the subclavian artery appeared to be compressed between the anterior end of the rib and the clavicle when the arm was abducted. Removal of the rib resulted in subsidence of the symptoms and a steady improvement of the blood supply to the arm.

The views as to the causation of vascular symptoms in cases of cervical rib are discussed. Evidence is given for the belief that the symptoms are secondary to damage to the arterial wall inflicted by the cervical rib.

The artery may be compressed by the cervical rib at the lateral border of the scalenus anticus or between the anterior end of the rib and the clavicle. It appears probable that the latter is the more common mechanism of compression.

HERBERT F. THURSTON, M.D.

BLOOD; TRANSFUSION

Takenouti, T.: The Change of the Circulating Blood Volume from Blood Transfusion and Infusion of Isotonic Gum-Arabic Solution in Normal as well as Splenectomized Rabbits (Veraenderung der zirkulierenden Blutmenge durch Bluttransfusion und Infusion von isotonischer Gummiloesung bei normalen sowie entmilzten Kaninchen). *Tohoku J. Exper. Med.*, 1940, 37: 517.

The transfusion of blood or intravenous infusions of colloidal solutions of gum-arabic and gelatin represent widely distributed therapeutic measures for the replacement of the blood volume in acute blood loss. It certainly is conceivable that when in anemia these solutions, which compared with other solutions such as Ringer solution or physiological saline solution are difficult to diffuse, are introduced into the circulation, they remain in the circulation for a longer time than the Ringer and physiological saline solutions and thus increase the circulating blood volume. However, the change caused by the infusions of the first mentioned solutions in cases in which there is no deficiency of the blood volume is of great interest, as well as the manner in which the organism overcomes the excess blood volume.

From previous experiments, it may be assumed that in blood transfusion, especially if excessive amounts of blood are deposited in various blood depots, some of the blood still remains in the circulation and the circulating blood volume is increased. However, the gum solution dilates the vessels more or less and differs from blood in its physicochemical structure. It displaces the blood present in the circulation, which necessarily results in a decrease of the circulating blood volume, but especially of the erythrocyte volume. The author has shown experimentally, that the spleen plays a predominant part as a blood depot in the regulation of the blood volume, and from this it may be assumed that the spleen plays a predominant part during blood transfusion or the infusion of gum solution into the circulation in the process of overcoming the excess of blood or gum solution. In the author's experiments, the effect of blood transfusion or infusion of gum solution in splenectomized rabbits on the circulating blood volume, plasma volume, and erythrocyte volume was compared with similar results in normal rabbits.

When excessive amounts of blood are injected into the circulation of normal rabbits, a small part of the added blood, although mostly deposited in the blood reservoir, remains in the circulation and necessarily results in an increase of the circulating blood volume. The fact that simultaneously the relationship of the plasma volume and erythrocytes is thrown out of balance (a relative increase of the latter) indicates that simultaneously with the deposition of the blood a part of the blood fluid streams into the tissues. This is an expression of the accommodating capacity of the organism to protect the heart from overloading with excessive blood.

Similar experiments on splenectomized rabbits showed that because the organism deprived of the spleen as a blood reservoir no longer has the capacity of storing excessive blood in the spleen, the regulation of the blood volume is insufficient.

The infusion of gum solution in normal rabbits showed that the infused gum solution forces a greater amount of blood, together with the erythrocytes, into the blood reservoir and remains in the circulation in place of the displaced blood. In this way

the relationship between the amount of plasma and erythrocytes in the circulating blood, in spite of the decrease of the circulating blood volume, undergoes a change, which expresses itself in an increase of the former and a decrease of the latter.

In splenectomized rabbits it was found that the infused gum solution forces a larger amount of blood together with the erythrocytes into the blood depots and remains in the circulation in its stead, and that with the absence of one of the blood depots into which the blood should be forced (the spleen), the amount of blood displaced is considerably less than when the spleen is present. Also the increase of the weight unit corresponding with the amount of plasma is greater than in the presence of the spleen. The fact that the erythrocyte volume does not decrease as much as in normal rabbits is indisputably attributable to the absence of the spleen, into which the erythrocytes should be forced.

Consequently much attention should be paid clinically to the condition of the spleen when a blood transfusion is to be undertaken. If, for example, a blood transfusion would be done on a splenectomized patient without due consideration in this respect, it would result in an excessive load on the heart as a result of a rapid increase in the amount of blood. When an infusion of gum solution is made, the blood is forced into the blood reservoirs and also decreases in amount because the spleen is a predominant blood depot. LOUIS NEUWELT, M.D.

Strumia, M. M., Wagner, J. A., and Monaghan, J. F.: The Intravenous Use of Serum and Plasma, Fresh and Preserved. *Ann. Surg.*, 1940, 111: 623.

The authors observe that although the number of contributions on this subject has greatly increased in the past few years, the intravenous use of serum and plasma in place of whole blood is not new. The purpose of this report is to emphasize the simplicity of preparation and the safety of the use of serum and plasma as compared to whole blood, and to make certain comparisons with the use of serum, both fresh and preserved.

The blood is collected in a closed system, a 2 per cent citrate solution in saline in the proportion of 100 c.cm. for each 500 c.cm. of blood being used as an anticoagulant. The blood is collected with a rather large needle and the aid of slight suction into a liter pyrex flask that contains the citrate-saline solution. The plasma is separated by centrifuging the citrated blood for about one-half hour at high speed. The average yield of plasma is a little over 50 per cent of the citrated blood employed, not including the added citrate-saline solution.

In the experience of the authors, it is not necessary to type the citrated plasma prior to intravenous administration. In over 1,500 administrations, there was complete safety and absence from reactions. A very important feature is that it can be given in very large and repeated doses. The plasma is diluted with equal parts of saline or saline-glucose solution and administered from 5 to 10 c.cm. per minute. If the bulk of fluids is to be limited, undiluted plasma may be administered safely.

It may be accepted as a fact that the intravenous administration of serum, fresh or preserved by the lyophile process, is often followed by severe reactions. These reactions were not encountered when citrated plasma, separated by centrifugation, was employed, fresh or preserved either by refrigeration or by the lyophile process. It is assumed that the difference is brought about by the process of fibrin precipitation.

In the ordinary type of hospital the lyophiling of plasma is not necessary, because of the fact that plasma keeps well under ordinary conditions of refrigeration (about 4°C.) for several months, except when used for its prothrombin and complement content. The content of specific antibodies in the plasma remains unchanged for at least thirty-two days; the complement activity begins to decline only after the third and fourth week. The period of useful survival of prothrombin was found to be from one week to ten days. Plasma preserved at 4°C. has been employed successfully after forty days in the treatment of secondary shock and various forms of hypoproteinemias. It is presumed that blood plasma can be preserved by refrigeration for much longer periods of time. Plasma has been kept for from three to four months in the frozen state, and then employed intravenously without reaction.

HERBERT F. THURSTON, M.D.

Downman, C. B. B., Oliver, J. O., and Young, I. M.: Partition of Potassium in Stored Blood. *Brit. M. J.*, 1940, 1: 559.

In blood stored according to current British Medical Research Council specifications the plasma potassium concentration rises rapidly during the first week to from five to ten times the initial level; thereafter the rise is comparatively slow. The source of this potassium is the red cell, from which it is liberated quite independently of hemolysis. At room temperature the plasma potassium concentration rises much less rapidly, reaching only 44 ± 7 mgm. per 100 c.cm. in six days. Reduction of the volume of diluent, absence of foreign salts, increase of oxygen tension, or storage at 38°C. did not reduce the rate of redistribution of the ion.

The present results show that the total amount of extracellular potassium in M.R.C. bottles stored at from 2° to 4° C. may be from 0.2 to 0.4 gm. within one week. This change is much greater than any other yet demonstrated in blood during the first two weeks of storage; and, whatever the clinical interest, it provides one useful index for comparing different methods of preserving blood for transfusion purposes.

It is known that potassium salts are toxic when administered in large amounts, the ion affecting particularly the cardiovascular system; for example, Thomson (1939) has recorded pronounced changes in the electrocardiogram when potassium salts were administered per os. There is, however, no clinical

evidence that the amount of potassium likely to be available in the volume of blood generally used for transfusion would be sufficient to produce toxic manifestations. Indeed, the absence of toxic symptoms in cases receiving large volumes of stored blood suggests that this repartition of potassium may be of minor clinical importance only.

The desire to find a means of limiting or preventing the repartition of potassium is only partially realized. The movement of the ion is considerably less at room temperature, but the possibility of infection is much increased and introduces an undesirable complication unjustifiable in practice.

J. THORNWELL WITHERSPOON, M.D.

Fischer, R., Alkalay, E., and Hochstætter, J.: Preserved Blood; the Effect of Blood Treated with Sangostat in Massive Hemorrhage (Sang conservé. L'action du sang sangosté sur les hémorragies massives). *Rev. méd. de la Suisse Rom.*, 1940, p. 157.

Fischer and his associates have previously reported on the value of preserved blood for clinical use. They have recently studied a new anticoagulant, sangostat, for the preservation of blood. Animal experiments have shown that severe hemorrhage may cause death by causing anemia of the nervous centers or by causing "true" anemia due to too great deficiency of the red cells. The latter form of fatal hemorrhage is rare. However, even if hemorrhage produces syncope it is not necessarily fatal, as there are considerable reserves of blood in the human body; the serums and other substitutes for blood employed in the treatment of shock due to hemorrhage are of value because they mobilize these reserves.

In experiments on rabbits, the effect of blood preserved with different anticoagulants was studied in the treatment of symptoms produced by bleeding. In order to avoid sudden cerebral anemia, the animals were bled with the head down. The carotid pressure was repeatedly recorded during the bleeding. In some experiments the preserved blood was injected when the pressure fell to 1½ or 2 c.cm. In others the bleeding was continued until convulsions occurred and the animal was in the death agony. In a third series of experiments, the preserved blood or fresh blood was injected when the carotid pressure fell to 2 c.cm. Then the animal was bled again till the pressure fell to zero, convulsions developed, and the heart was in fibrillation; then fresh blood or preserved blood was injected again. It was found that preserved blood treated by various types of anticoagulants could save the life of the animal when near the death agony. If given when the pressure was falling and the animal was in syncope, a much smaller quantity of blood was required. If such a large quantity of blood had been withdrawn that the life of the animal could not be saved by the injection of preserved blood, it was also found impossible to supply the blood loss and revive the animal with the transfusion of fresh blood.

With sodium citrate or heparin as an anticoagulant, preserved blood is not effective if it has been preserved more than eight days; if sangostat is used as the anticoagulant, it is effective if preserved for fifteen days. The amount of blood necessary also varies with the anticoagulant used. Too large a quantity of preserved blood should not be employed in the treatment of massive hemorrhage; this is true also of fresh blood, as large amounts may cause death by shock or embolus. The quantity employed should be just sufficient to raise the blood pressure to a satisfactory level. In a case reported, an injection of 150 c.cm. of preserved blood treated with sangostat was sufficient to raise the blood pressure and bring the patient out of coma after an internal hemorrhage; this patient died later because of a generalized thrombophlebitis. The preserved blood is of value not merely to supply the blood loss, but because it mobilizes the reserve supplies of the body. In cases of severe hemorrhage, the transfusion of preserved blood is as effective as that of fresh blood in overcoming shock and syncope and raising the blood pressure; if the hemorrhage continues, the injection of preserved blood raises the pressure sufficiently until a large transfusion can be given and the patient prepared for any operation that may be necessary. ALICE M. MEYERS.

SURGICAL TECHNIQUE

OPERATIVE SURGERY AND TECHNIQUE; POSTOPERATIVE TREATMENT

DeTakats, G., and Jesser, J. H.: Pulmonary Embolism. *J. Am. M. Ass.*, 1940, 114: 1415.

A large collected series of cases of pulmonary embolism reveals a fairly steady incidence in large services, namely from 0.1 to 0.2 per cent of all operations, 2 per cent of all deaths, 6 per cent of postoperative deaths, and about 10 per cent of all autopsies. In the present report the authors confine their remarks largely to observations on the value of early diagnosis and the employment of simple procedures which may reduce the incidence and high mortality. In a series of 100 cases which showed undoubted evidence of thrombophlebitis or hemoptysis, roentgen evidence of infarction, or were proved at autopsy, there were 25 medical cases, 74 surgical cases, and 1 obstetrical case. Of the medical patients 18 had heart disease, and 33 treated surgically had been subjected to pelvic laparotomy.

The initial signs and symptoms most frequently noted were dyspnea, chest pain, cyanosis, weak, rapid pulse, shock, and restlessness. Abdominal symptoms suggesting acute cholecystitis or ruptured viscus were observed. Likewise cerebral anemia signified by convulsions or vertigo were frequent. The conception that the survival time following pulmonary embolism is too brief to institute therapeutic efforts is erroneous as shown by the fact that in the group of 70 fatal embolisms 8.5 per cent of the patients died in less than ten minutes, roughly 60 per cent lived more than one hour, and 34 per cent lived from one to several days.

Of the precipitating factors most commonly noted, bowel movement and active or passive physical exertion head the list, but in 70 cases no obvious precipitating factors could be elicited and in these possibly physiochemical changes played important rôles.

Eighty-seven patients in this series died, while 13 recovered. A large number had more than one infarct, and the authors estimated that a patient who survived one pulmonary embolism had a 40 per cent chance of having another one; but if he survived the second he would have only a 12 per cent chance of having any more.

On the basis of experimental observations the authors believe that a widespread radiation of autonomic reflexes occurs during pulmonary embolism which may contribute to the causes of death. The vagus constricts the smooth muscles of the coronaries, the bronchi, and the upper gastro-intestinal tract. It is suggested that atropine be used to block the vagus impulses and papaverine to relax the contracted smooth muscle.

Factors predisposing to postoperative thrombosis are: increase in the number of platelets which occurs following any major operation and reaches its peak between the eighth and eleventh days; increase in the fibrinogen; a shift of the albumin-globulin ratio in favor of the globulins; and an increase in blood viscosity. The increase in platelets and leucocytes results in liberation of thrombokinase and hastens the coagulation of stagnating blood adjoining an obstructing platelet thrombus.

The importance of clean, sharp dissection and avoidance of undue trauma to the tissues is stressed. Other factors to be considered are age, overweight, and operations on the lower part of the abdomen, pelvis, and the lower extremities. Too little attention has been paid to counteracting the marked retardation of the blood flow which occurs after every major operation and after childbirth. The veins of the pelvis and lower extremities are the most favorable sites for stasis. Immobilization in bed, superficial breathing, intestinal distention, tight abdominal binders, and motionless rigidity due to postoperative pain are all factors which interfere with venous backflow. Various means have been described to improve the circulation, and among these are exercises of the legs; turning the patient from side to side; deep breathing exercises; administration of thyroid extract; digitalization of the failing heart; and the postoperative Trendelenburg position. The authors find the latter a worthwhile adjunct except when intra-abdominal suppuration or cardiac failure contraindicates its use. They have also found that the use of a set of mounted bicycle pedals used for five minutes three times a day aids the return venous flow.

It must be recognized that a correct diagnosis is not always made, and only measures which would do no harm even if pulmonary embolism is not present should be used. When cyanosis and dyspnea are predominant oxygen is indicated. One hundred per cent oxygen administered with the BLB mask is preferable. In the syncopal type of embolism, characterized by pallor, fall in the blood pressure, and retrosternal pain without cyanosis, papaverine and atropine are advocated. Both drugs are given intravenously and it is desirable to dissolve the drugs in saline just before administration. Papaverine is given in doses of ½ gr. (0.03 gm.) and atropine in doses of from 1/60 to 1/75 gr. (from 0.001 to 0.0008 gm.).

The successful removal of the obstructing plug in the pulmonary artery has been possible only 9 times in 132 attempts, and recently Pilcher has suggested that the slowly dying patients might be operated on two or three hours after the onset of the symptoms while not in a moribund state but showing no improvement. Another surgical procedure is suggested which entails the removal of a recognizable localized clot in one of the ileofemoral veins through the saphenous vein.

JOHN A. GIUS, M.D.

ANESTHESIA

Hediger, E. M., Chenoweth, M. B., and Gold, H.: The Use of Bulk Ether in Surgical Anesthesia. *J. Am. M. Ass.*, 1940, 114: 1424.

The belief prevails that U.S.P. anesthetic ether deteriorates very quickly and is unfit for anesthesia twenty-four hours after the container is opened. It has previously been reported that this view is based on a misconception, and further clinical and chemical studies now reported show that ether does not deteriorate nearly as quickly as is commonly supposed. If the sealed metal container in which anesthetic ether is supplied is opened and the container stoppered with a cork repeatedly, the ether remains pure for many weeks. Cork which may fall into the ether or air which may gain access to it exert no appreciable influence on the speed of its deterioration. In a series of nearly 2,000 surgical anesthesias in which ether was used it was found that ether from cork-stoppered anesthetic ether cans was indistinguishable clinically from ether in sealed metal containers.

From these findings the authors conclude that hospitals may use bulk ether for anesthetic purposes without compromising the purity of the ether or the safety of the patient. A considerable saving in the cost of ether can thus be effected.

JOHN A. GIUS, M.D.

Popoff, A. F.: Experimental Fractional Spinal Anesthesia. *Vestnik khir.*, 1940, 59: 101.

With the usual technique of spinal anesthesia the concentration of the drug introduced into the spinal canal may be insufficient in some cases while in others an overdose may produce serious symptoms. An individual dose can be properly selected only if the fractional method of injection is used. The author employed this method in 50 cats.

After urethan anesthesia a laminectomy was performed to allow an introduction of the anesthetic solution into the spinal canal under eye control. The blood pressure and respiration were recorded with the technique customary in animal experimentation. A 2 per cent novocain solution used for spinal anesthesia was introduced in 7, 8, or 9 equal or rising doses in the lumbar segment of the spine. After the introduction of the first fraction the blood pressure became stabilized and responded less to repeated injections. In this manner a total dose of the anesthetic from 5 to 9 times as large as a single fatal dose, was well tolerated. An addition of ephedrin increased the tolerance still more. A prophylactic injection of ephedrin diminished the fall of the blood pressure following the first injection of the anesthetic and stabilized the tonus of the blood vessels.

The fractional method of spinal anesthesia eliminates the shock of the nervous system provoked by the customary single injection of a large dose of the anesthetic solution. Furthermore, dangerous symptoms can be noticed sooner when the fractional method is employed. Among fatal sequelæ of the spinal anesthesia, the disturbance of respiration occupies the main place and it is therefore important that the attention of the anesthetist be concentrated on observation of the respiration.

JOSEPH K. NARAT, M.D.

SURGICAL INSTRUMENTS AND APPARATUS

Evstropoff, A. P.: Parietal Catgut. *Nov. khir. arkh.*, 1939, 45: 104.

Numerous publications describe difficulties encountered in perfect sterilization of common catgut and therefore a search for a less infectible absorbable material is fully justified.

Kuznetzoff introduced so-called neocatgut prepared from the serous membranes of the bovine cecum. The serosa is removed from the gut after its eventration, care being taken to avoid any incision into the lumen of the intestines. However, the rapid multiplication of the intestinal flora post mortem may be responsible for a contamination of the inner layer of the serosa. Therefore, the author of this article prefers the use of parietal peritoneum. Strips of it 60 by 80 cm. are cut out after a preliminary removal of the abdominal contents, without opening of the intestinal lumen. The peritoneum, removed together with the preperitoneal fascia, is placed for at least twenty-four hours in a 1 per cent aqueous formalin solution. After that the strips are washed in running water for from ten to fifteen minutes and spread on glass. The preperitoneal fascia is separated from the peritoneum within the area of the elastic reticulum. The remaining tissue, 0.01 to 0.02 mm. thick, is divided into strips from 1 to 3 cm. wide which are braided and dried under tension. After twenty-four hours they are ready for use.

Laboratory studies of dry and wet parietal catgut showed that the variations in the diameter of the dried material are one and one-half times as great as those of the common catgut, while the diameter of the wet catgut remains more uniform. The tensile strength of parietal catgut is one and one-half times less than that of common catgut. The resorption of the new material is twice as slow as that of the intestinal catgut. This is a great advantage because the strength of an intestinal catgut suture diminishes on the third to sixth day while the parietal catgut retains its strength for from nine to twelve days. After sterilization according to Claudius' method parietal catgut becomes elastic, knots can be tied easily, and the suture material is not as slippery as intestinal catgut. The preparation of the new type of catgut requires only one or two days.

JOSEPH K. NARAT, M.D.

PHYSICOCHEMICAL METHODS IN SURGERY

ROENTGENOLOGY

Oppenheimer, A.: The Ileocecal Region. *Radiology*, 1940, 34: 545.

Since 1928 the author has observed the ileocecal region systematically in routine examinations whenever possible and published some of his observations in previous papers. The present report is confined to an analysis of records obtained in 86 persons, apparently healthy. Special attention was given to the following questions:

1. How is the food moved on from the ileum into the cecum?

2. How does the food ascend through the cecum and proximal colon?

3. Is there any correlation between this kind of peristalsis and the passage of food through the ileocecal valve?

4. Does the ileocecal valve control the passage actively, by sphincteric contractions, or does it merely yield to pressure, like a valve?

The methods employed in the study are described briefly. Observations were made at varying intervals after an opaque meal of the terminal ileum, cecum, ileocecal valve, cecocolonic sphincter, and appendix, and the findings are recorded in detail. The results are summarized as follows:

1. Both in the terminal ileum and in the cecum and ascending colon, opaque food is moved on chiefly by "systolic" tonic contractions which are preceded by "diastolic" relaxations due to loss of tone. The tonic variations are fairly rapid in the terminal ileum, but very slow in the ascending colon; in the latter, the caudad progression of the haustra helps to carry the food upward as though by a dredging device.

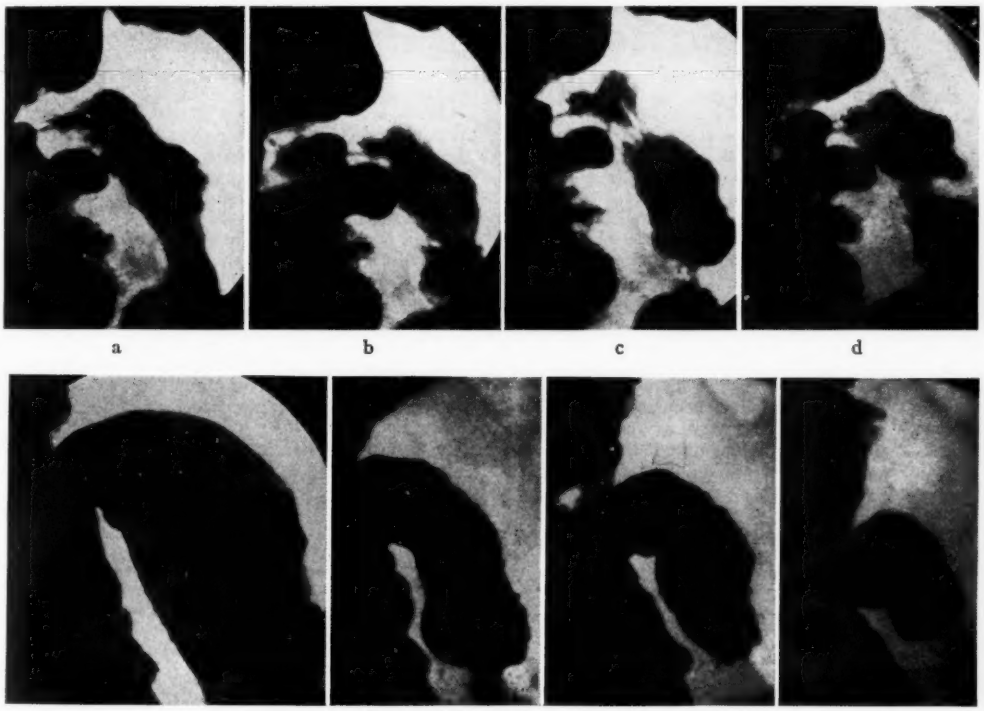

Fig. 1. Upper row 1-a through 1-d: rhythmic peristalsis in terminal ileum, ileocecal valve closed; no barium enters the cecum. Lower row, 1-e through 1-h: after a sudden relaxation (1-e) the terminal ileum is emptied by one single stripping contraction (1-f through 1-h). Spot films taken at intervals of from seven to nine seconds. The two series show that food is moved on into the cecum by means of changes in tone, but not by rhythmic peristalsis.

2. Rhythmic peristalsis does not move the contents appreciably, unless it occurs as a stand-by mechanism.

3. A "receptive relaxation" of the cecum begins as soon as opaque food reaches the ileal loops proximal to the terminal loop.

4. The cecum is normally low in position when it begins to fill, and rises while the contents are moved on into the transverse colon.

5. The ileocecal valve remains closed while peristalsis in the terminal ileum is wave-shaped and rhythmic; it becomes passable when the opaque medium is driven forward by tonic "stripping" contractions in the terminal ileum. The valve is normally competent for opaque food given by mouth.

6. The cecocolonic sphincter is relaxed while the ascending colon fills, but contracts strongly while mass peristalsis drives the contents into distal parts. This contraction causes a physiological stasis in the cecum.

7. The vermiform appendix is filled by the peristalsis of the cecum, but is emptied by its own intrinsic tonic contractions.

ADOLPH HARTUNG, M.D.

Tod, M. C.: The Treatment of Metastases. *Brit. J. Radiol.*, 1940, 13: 163.

Radiotherapy for metastases differs according to whether treatment can be expected to cure or only to palliate the symptoms. Curability depends greatly upon whether the neoplastic cells have reached the site of secondary deposit by lymphatic or hematogenous spread. In the case of lymphatic spread, areas likely to be involved can be foretold with some certainty, and treatment of these areas, if limited to regions where curative dosage is possible, may result in destruction of such cells and may prevent dissemination. It is impossible to forestall the appearance of blood-borne metastases either before they appear or after the detection of a solitary deposit, so treatment must in general be palliative.

Curability also depends largely upon the radiosensitivity of the particular neoplasm. A biopsy diagnosis is usually necessary to determine this sensitivity, but it may be estimated either by giving a small dose to the whole lesion or a larger dose to a small part of the tumor, and watching the effect. Metastases from two groups of tumors are susceptible to curative therapy: highly radiosensitive tumors which call for treatment of large volumes at low dosage, and tumors of limited sensitivity, a group which includes the familiar squamous-cell carcinoma and most of the carcinomas of the breast. These must be treated with higher doses and, therefore, in small volumes. Treatment of metastases from resistant tumors, such as the sarcomas of adult tissue, is never curative.

The following conditions are listed as probably being highly sensitive:

1. Tumors of embryonal origin:
   - Seminoma testis
   - True embryonal tumor of the ovary
2. Primitive tumors of unknown origin:
   - Wilms' tumor of the kidney
   - Some tumors of the thyroid glands
   - Some tumors of the salivary glands
   - Some tumors of the nasopharynx and nasal accessory sinuses
3. Conditions of reticulo-endothelial origin:
   - Leucemia
   - Hodgkins' disease (lymphadenoma)
   - Lymphosarcoma (reticulosarcoma)
   - Thymoma
   - Ewing's tumor
   - Endothelioma of vascular origin
   - Miscellaneous reticulo-endothelial diseases

The propriety of including in this list some of the reticuloses, which are generalized diseases, is discussed briefly.

As regards the method of treatment in regional therapy for tumors of high sensitivity, the aim should be to deliver to the whole region likely to be involved, doses of radiation which should prove lethal to the tumor without exceeding the general tolerance. Detailed information and diagram illustrations are included to exemplify the methods used. Blood counts are considered essential as an index of the general tolerance. The development of radiation sickness is discussed and means for its avoidance or reduction are given consideration.

Localized therapy for metastases from tumors of limited sensitivity is essentially a question of dose. The common accessible tumors nearly all belong to this class, and experience has proved that when an attempt is made to cure squamous-cell or columnar-cell carcinoma a certain minimum dose must be attained if there is to be any hope of success. The dose required is such that the volume of tissue which can be treated is strictly limited by local tolerance. Operable metastases from such lesions should preferably be treated by operation.

For palliative therapy of metastases, the following techniques are listed and discussed at some length:

1. Localized therapy for single deposits of sensitive neoplasms when more foci are known to be present.

2. A growth-restraint technique for resistant tumors.

3. A "chasing" technique which treats individually a series of secondaries as they appear.

4. Symptomatic palliative therapy.

ADOLPH HARTUNG, M.D.

Den Hoed, D.: The Supervoltage Roentgen Installation in the Antoni van Leeuwenhoekhuis at Amsterdam. *Acta radiol.*, 1940, 21: 32.

An ever-increasing number of roentgen therapeutic apparatus operating at tensions of from 400 to 600 kv. are being built and, recently, apparatus operating at tensions up to 1,000 kv. (thus approaching the penetrating power of the radium rays) are being built, especially in America. In connection with such installations, particular attention must be paid to new physical and biological problems.

1. A study of the physical problems leads to the conclusion that the supervoltage roentgen therapy is more advantageous than the deep roentgen therapy because of (a) the greater penetrating power of the rays; (b) the greater depth-dose in water; (c) the possibility of using smaller fields in practice; (d) the smaller volume-dose; (e) the flatter isodose curves; (f) the higher output of radiation; and (g) the change of quality in deeper layers. However, the importance of the last is questionable.

2. The biological advantages are that comparatively larger surface doses may be administered to obtain the same erythema than with deep roentgen therapy, and that thus there is less damage to the skin. It also appears that the efficacy of the irradiation as a whole is greater.

Recently the author has installed at the Antoni van Leeuwenhoekhuis a supervoltage roentgen-therapy apparatus which theoretically is capable of operating at 1,200 kv., but which for the sake of safety is being run for the time being at 850 kv. The principles of this apparatus as well as the arrangement of the treatment room are briefly discussed.

The high-voltage source consists of a cascaded type generator of the Greinacher, Cockroft, and Bouwers circuit, with one end grounded. The valves are oxide cathode gas-filled rectifiers, requiring only 8 watts of heating energy.

The roentgen tube is three-sectional, the individual sections being soldered together after separate outgassing. The partitions, composed of constantan foils, are permeable to the electron beam. Each of the sections can withstand a tension of 400 kv., so that the tube is designed for 1,200 kv. The filament is at one end of the tube fed by batteries, and the target at the other end. The electron beam is focused on the target by means of several electromagnets at various points along the tube. One of the essential features of construction is the fact that several reservoirs of "getters" chemical compounds, which have a strong absorbing power for gases, are fitted within each section of the tube. When gas is formed at the time of the original sealing or later during the long run of the tube, the electric explosion of a "getter" restores the vacuum within a short time.

The entire generating plant is mounted in a cellar which is 5 meters deep, 8 meters long, and 5 meters wide, in order to insure satisfactory protection. Apertures are provided in the ceiling for the simultaneous treatment of 3 patients, who are placed in a room on the ground floor on couches with parallel longitudinal axes. The walls of the treatment room, as well as the control cabinet are heavily protected with barium concrete and lead screens.

The output of the roentgen tube was measured as 6-7 roentgen min. at 125 cm. distance with 825 kv. 2 mm. copper, ½ mm. tin and ½ mm. aluminum as filters and 0.9 ma. as tube current. The half-value layer under these conditions proved to be 5.9 mm. of copper.

The clinical results will be reported in subsequent articles. T. Leucutia, M.D.

MISCELLANEOUS

CLINICAL ENTITIES—GENERAL PHYSIOLOGICAL CONDITIONS

Uggeri, C., and Rossi, B.: A Contribution to the Study of Subcutaneous Sarcoma (Contributo allo studio della sarcomatosi ipodermica). *Clin. chir.*, 1940, 16: 263.

Of the numerous classifications of cutaneous sarcoma, the authors cite those of Perrin and Unna as the most generally accepted. Perrin classifies sarcomas into primary and secondary. The primary group comprises Kaposi's type, Perrin's type, and an atypical or intermediate form. The secondary cutaneous sarcomas, which originate from warts, moles, healthy skin, or other organs, are progressive in growth and have a variable clinical and histological character. The survival period in this latter type seldom exceeds two years. The authors, however, prefer the classification of Unna into regular sarcoma (idiopathic sarcoma of Kaposi and melanotic sarcoma) and irregular sarcoma types described by Pifford, Unna, Perrin, Neumann, Funk Hyde. These various types are briefly described.

The authors describe a case of subcutaneous sarcoma developing in a sixty-five-year-old farmer about one and one-half months following recovery from an attack of influenza. There was a mass about the size of a pigeon's egg on the lower lateral side of the left hemithorax. Within seven weeks the mass increased rapidly in size and another developed beneath and anterior to the first, ovoid in shape, about 12 by 7 or 8 cm. in size, and reddish gray in color. The mass was slightly mobile, hard, and parenchymatous in consistency and caused slight pain on pressure. The entire mass including the skin was excised and the wound healed within twelve days.

Several days after operation, numerous similar nodules (about 100) appeared on the trunk and neck. The roentgen-ray examination revealed the absence of visceral involvement. Intense arsenic therapy had no effect. Irradiation therapy had a slight effect but did not reduce the size of the nodules. The patient's general condition gradually became worse and he died about four and one-half months following operation. Histological examination demonstrated a polymorphous cellular sarcoma, with a predominance of spindle cells.

The authors cite 4 cases in the recent literature which were similar to their case. These cases were characteristic of Perrin's type regarding the location, distribution, and clinical course, but histologically they differed in that most of the cells were spindle-shaped instead of round.

The authors point out that the origin of these tumors is still a controversial subject. The various origins that have been considered, i.e., fibroblastic, neurogenic, vascular, and endothelial, are reviewed. The authors concluded that the sarcoma in their case was probably of reticular or histiocytic origin.

MICHAEL DEBAKEY, M.D

Santagati F.: Sarcoma of the Reticulo-Endothelial System (Il Retotelsarcoma). *Tumori*, 1940, 26: 48.

Radiologists have recently been devoting more attention to the tumors of the reticulo-endothelial system, especially those involving the lymphatic tissues. Of particular interest has been the group of reticulosarcomas.

The author reviews the literature of reticulosarcoma from the time of Virchow down to the present. He reports on 58 cases treated since 1928 at the Tumor Clinic of the Milan University. Histologically, reticulosarcomas result from the malignant hyperplasia of the reticular elements of the lymphatic glands or tonsils. According to Edling, these tumors form 11.5 per cent of all tumors of the lymphatic tissues.

The author's group of 58 cases was gathered between 1928 and 1939 and consisted of 34 cases of tumors involving the tonsils and rhinopharyngeal region, and 24 cases of tumors localized in the lymph glands elsewhere in the body. Reticulosarcoma appears to be most common during adolescence; the youngest patient was nine years old, the oldest seventy-six years. In the author's series 60 per cent of those affected were males. The tumors were malignant and tended to progress although the degree of malignancy varied in individual cases. The most common localization was in the glands of the neck, pharynx, and tonsils. The author noted that in some of his cases the condition was preceded by an acute tonsillitis or tonsillar abscess. There was a mild intermittent febrile reaction which in some cases led to a diagnosis of tuberculosis or lymphogranuloma. With progressive development of the tumor loss of appetite, asthenia, and cachexia occurred. The blood showed a mild anemia; the white cells were normal or moderately increased; 1 of the author's cases showed the formula of a lymphatic leucemia.

With tonsillar localization the patient had the sensation of the presence of a foreign body when swallowing. There were otalgia, sialorrhea, and enlargement of the glands in the neck. Deglutition became painful and difficult and the patient was forced to take liquid and semi-liquid food. The tonsil was enlarged in volume with infiltration of the tissues in the vicinity.

The differential diagnosis must include consideration of simple hypertrophy, ulcerated gumma, tuberculosis, lymphoid leucemia, and lymphogranuloma. Glandular metastases develop early and in tumors of the tonsillopharyngeal region may be the first evidence of the condition. Metastases have been encountered in the pleura, liver, ribs, vertebral column,

intestine, lungs, vagina, pancreas, kidneys, and adrenal and thyroid glands.

As to treatment, the author refutes surgery and favors radiation with the x-rays or radium. The tumors are very sensitive to radiotherapy. For epipharyngeal tumors Zuppinger gives from 3,500 to 4,000 roentgens per field. On the other hand, Eigler and Koch report a case treated with 250 roentgens which remained cured after six years. The author uses from 1,500 to 3,000 roentgens. He also uses from 160 to 170 kv., a distance from 40 to 50 cm., and a filter from 0.5 to 1 mm. of copper plus 1 mm. aluminum. For the glandular types the author prefers roentgenotherapy to radium. For the epipharyngeal tumors he uses both radium and x-ray treatments. The former is given by means of a tube of 10 mgm. of radium in the rhinopharynx with a dose of from 7 to 8 mcd.

A variety of results are reported in the literature. Beck reported 20.8 per cent of his patients cured after three years. The author gives a detailed tabulation of his cases and results. The immediate results of the author's 58 cases were brilliant: 88 per cent showed complete regression of the neoplasm after radiation therapy, while only 12 per cent terminated fatally during the first treatment or shortly after. There were 23 recurrences noted within the first six months after treatment. Of 34 patients in the orotonsillopharyngeal group 18 have died and 16 are still alive. Of 24 patients with conditions of the primary glandular group only 3 have remained free of disease for a period of from one to two years. Of the 19 deaths in the latter group 3 occurred within from twelve to twenty months after the beginning of treatment, 3 after ten months, and all the others in less than six months. In the tonsillo-oropharyngeal group there were 6 one-year cures (40 per cent), and in the primary glandular group there were one-year cures in 25 per cent of the cases. The author comments that in the primary involvement of the lymph glands extraordinary malignant types have been observed.

The author concludes that these tumors represent a definite clinico-anatomical entity, that they occur with relative frequency, and that they are probably identified with the so-called lympho-epitheliomas. The diagnosis should always be controlled by biopsy; the prognosis should be reserved because of the tendency toward recurrence and metastases, particularly in the primary glandular forms. The surgical treatment of such tumors should be abandoned. Finally, although the immediate results of radiation therapy are brilliant, the later results after one and two years are doubtful. JACOB E. KLEIN, M.D.

Allen, J. G., and Julian, O. C.: The Clinical Use of a Synthetic Substance Resembling Vitamin K (2-Methyl-1, 4-Naphthoquinone). *Arch. Surg.*, 1940, 40: 912.

The synthetic substance, 2-methyl-1, 4-naphthoquinone, in dosage of 8 mgm. per day by mouth, rapidly reduced the prothrombin time to normal in 4 cases of obstructive jaundice, 1 case of biliary fistula, 1 of sprue, and 1 of hepatitis, but was completely ineffective in a case of acute yellow atrophy and 2 cases of cirrhosis of the liver. In the last even intravenous injection was without effect. This suggested that in advanced liver disease the process of activation of the prothrombin by the naphthoquinone failed to occur. PAUL STARR, M.D.

DUCTLESS GLANDS

Guszich, A.: Studies on Serum Lipase in Operations (Serumlipase-Untersuchungen bei Operationen). *Orvosképzés*, 1939, 29: 322.

The undisturbed state of the thinning of the skin is assured by the lipase and the bile together. The basic principle of the studies on serum lipase was the establishment of the fact that organ-specific lipases penetrate into the blood only in diseases or injuries of very definite organs. In a series of experiments it was intended to determine, not the absolute amount of the serum lipase, but the relationship of the lipase to the blood before and after certain operations. For this purpose, patients of three disease groups were selected, namely: (1) those with disease of organs that are distant from the pancreas (the control studies were made forty-eight hours after the operation); (2) those with carcinoma; and (3) those with disease of the stomach, duodenum, and biliary passages, and with acute and chronic pancreatitis.

In summarizing the results of these investigations, the author shows that the operations that were made on organs that were distant from the pancreas did not essentially affect the function of the pancreas. The increase in lipase after operations on the stomach, duodenum, and the biliary passages indicates a transient, organic, and not functional disturbance of the gland, chiefly the result of the mechanical insult produced by the operative trauma. Relatively often pancreatic changes are associated with cholelithiasis and also with diseases of the biliary passages; in these cases the tenderness traceable to the left side (gall stone), and the increase of the serum lipase, should be determined; the latter draws attention to the seriousness of biliary disease.

Patients with cholelithiasis are always exposed to the danger of disease of the pancreas, concerning the prognosis of which nothing definite can be said beforehand. In other words, the symptoms originating from a gall stone may recede with conservative treatment, but a final cure can be expected only with surgical therapy. The gall stone may lead to pancreatitis through mechanical or bacterial means or through reflexes. In addition to a pus-producing gall bladder containing bacteria, toxic injury of the pancreas is always probable.

In chronic cases, in which operation (cholecystectomy, opening of an abscess) resulted in an improvement of the disease symptoms, a diminution of the lipase values was usually observed. In carcinomatous cases with higher lipase values after a

radical operation, a tendency toward lowering of the lipase values was observed. There is no kind of parallelism between lipase and diastase, but the lipase reaction is a relatively more sensitive method for the determination of pancreatic diseases. Necrosis of the pancreas may recede with expectant treatment, but it is difficult to determine whether in certain cases a milder or severer course is to be expected. Nor do the ferment values give any reliable information regarding the course of the condition. It is possible that in cases that improve on simple bed rest, extreme variations of the ferments may be found, while in rapidly progressing severe cases, no changes are found. When the diastase content of the urine, or the lipase content of the blood is not increased, attention must be paid to the blood-sugar content. That sometimes no ferment change is found in severe pancreatic changes is due to the fact that the variation observed in the ferments is only a very delicate sign (indicator) of the reactionary changes of the organ, i.e., it is a physicochemical reaction indicating the basic changes of the colloids.

Further conclusions cannot be drawn from the changes in the ferment values; abnormally high values indicate pancreatic disease, but their absence does not deny it. These results can be evaluated only on the basis of a careful clinical observation.

(E. Illés). Louis Neuwelt, M.D.

Roncoroni, C., and Casacci, A.: The Functional Relationship Between the Di-Encephalohypophyseal System and the Thyroid Investigated by Means of the Changes Induced in the Basal Metabolism by Spinal Puncture (I rapporti funzionali fra sistema diencefalo-ipofisario e tiroide esplorati per mezzo delle modificazioni indotte dalla rachicentesi sul metabolismo basale). *Riforma med.*, 1940, 56: 306.

The authors performed experiments on three groups of subjects: individuals with increased, decreased, and normal basal metabolisms. The experiments included a preliminary determination of the basal metabolism of the fasting subject, a spinal puncture followed by subtraction of from 12 to 15 c.cm. of cerebrospinal fluid, and further determinations of the basal metabolism one-half hour, one hour, two hours, and twenty-four hours after the puncture. In order to find out whether simple puncture of the meninges was sufficient to cause changes in the basal metabolism, the same sequence of events was followed in a control group, but no cerebrospinal fluid was subtracted after the puncture had been made. Possible causes of error due to the emotional state of the subject were avoided by making basal metabolism determinations on several days preceding the experiment.

Spinal puncture with subtraction of cerebrospinal fluid regularly caused an increase in the basal metabolism determined one-half hour after the intervention. The higher the initial basal metabolism, the more pronounced became the increase. In hyperthyroid subjects, the return to normal of the basal metabolism occurred much more slowly than in subjects with a normal basal metabolism. In subjects with a decreased basal metabolism, a subsequent decrease occurred after an initial temporary increase. The metabolic values had returned to their starting point in all subjects after twenty-four hours. Simple lumbar puncture without subtraction of cerebrospinal fluid did not cause any changes in the basal metabolism.

The authors think that it is possible that in subjects with altered basal metabolisms the spinal puncture induces a subsequent deviation from the normal in accordance with the metabolic tendency of the individual, and they believe that the spinal puncture acts probably through a disturbance of the pressure in the third ventricle which has its repercussion on the di-encephalic nuclei.

Richard Kemel, M.D.